(51) International Patent Classification [5] :		(11) International Publication Number:	WO 94/17185
C12N 15/27, C07K 3/00, C12P 21/02, C07K 13/00, G06F 15/60	A1	(43) International Publication Date:	4 August 1994 (04.08.94)

(21) International Application Number: PCT/US94/00913

(22) International Filing Date: 25 January 1994 (25.01.94)

(30) Priority Data:
08/010,099   28 January 1993 (28.01.93)   US

(71) Applicant: AMGEN INC. [US/US]; Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789 (US).

(72) Inventor: OSSLUND, Timothy, D.; 475 Vista Montana, Camarillo, CA 93010 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen Inc., Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789 (US).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: G-CSF ANALOG COMPOSITIONS AND METHODS

(57) Abstract

Provided herein are granulocyte colony stimulating factor ("G-CSF") analogs, compositions containing such analogs, and related compositions. In another aspect, provided herein are nucleic acids encoding the present analogs or related nucleic acids, related host cells and vectors. In yet another aspect, provided herein are computer programs and apparatuses for expressing the three dimensional structure of G-CSF and analogs thereof. In another aspect, provided herein are methods for rationally designing G-CSF analogs and related compositions. In yet another aspect, provided herein are methods for treatment using the present G-CSF analogs.

- 1 -

G-CSF ANALOG COMPOSITIONS AND METHODS

Field of the Invention

This invention relates to granulocyte colony
5   stimulating factor ("G-CSF") analogs, compositions
containing such analogs, and related compositions. In
another aspect, the present invention relates to nucleic
acids encoding the present analogs or related nucleic
acids, related host cells and vectors. In another
10 aspect, the invention relates to computer programs and
apparatuses for expressing the three dimensional
structure of G-CSF and analogs thereof. In another
aspect, the invention relates to methods for rationally
designing G-CSF analogs and related compositions. In
15 yet another aspect, the present invention relates to
methods for treatment using the present G-CSF analogs.

Background

Hematopoiesis is controlled by two systems:
20 the cells within the bone marrow microenvironment and
growth factors. The growth factors, also called colony
stimulating factors, stimulate committed progenitor
cells to proliferate and to form colonies of
differentiating blood cells. One of these factors is
25 granulocyte colony stimulating factor, herein called
G-CSF, which preferentially stimulates the growth and
development of neutrophils, indicating a potential use
in neutropenic states. Welte et al., PNAS-USA 82: 1526-
1530 (1985); Souza et al., Science 232: 61-65 (1986) and
30 Gabrilove, J. Seminars in Hematology 26: (2) 1-14
(1989).

In humans, endogenous G-CSF is detectable in
blood plasma. Jones et al., Bailliere's Clinical
Hematology 2 (1): 83-111 (1989). G-CSF is produced by
35 fibroblasts, macrophages, T cells trophoblasts,
endothelial cells and epithelial cells and is the

- 2 -

expression product of a single copy gene comprised of
four exons and five introns located on chromosome
seventeen. Transcription of this locus produces a mRNA
species which is differentially processed, resulting in
5   two forms of G-CSF mRNA, one version coding for a
protein of 177 amino acids, the other coding for a
protein of 174 amino acids, Nagata et al., EMBO J 5:
575-581 (1986), and the form comprised of 174 amino
acids has been found to have the greatest specific in
10   vivo biological activity. G-CSF is species cross-
reactive, such that when human G-CSF is administered to
another mammal such as a mouse, canine or monkey,
sustained neutrophil leukocytosis is elicited. Moore et
al., PNAS-USA 84: 7134-7138 (1987).

15   Human G-CSF can be obtained and purified from
a number of sources. Natural human G-CSF (nhG-CSF) can
be isolated from the supernatants of cultured human
tumor cell lines. The development of recombinant DNA
technology, see, for instance, U.S. Patent 4,810,643
20   (Souza) incorporated herein by reference, has enabled
the production of commercial scale quantities of G-CSF
in glycosylated form as a product of eukaryotic host
cell expression, and of G-CSF in non-glycosylated form
as a product of prokaryotic host cell expression.

25   G-CSF has been found to be useful in the
treatment of indications where an increase in
neutrophils will provide benefits. For example, for
cancer patients, G-CSF is beneficial as a means of
selectively stimulating neutrophil production to
30   compensate for hematopoietic deficits resulting from
chemotherapy or radiation therapy. Other indications
include treatment of various infectious diseases and
related conditions, such as sepsis, which is typically
caused by a metabolite of bacteria. G-CSF is also
35   useful alone, or in combination with other compounds,
such as other cytokines, for growth or expansion of

- 3 -

cells in culture, for example, for bone marrow
transplants.

Signal transduction, the way in which G-CSF
effects cellular metabolism, is not currently thoroughly
5   understood. G-CSF binds to a cell-surface receptor
which apparently initiates the changes within particular
progenitor cells, leading to cell differentiation.

Various altered G-CSF's have been reported.
Generally, for design of drugs, certain changes are
10   known to have certain structural effects. For example,
deleting one cysteine could result in the unfolding of a
molecule which is, in its unaltered state, is normally
folded via a disulfide bridge. There are other known
methods for adding, deleting or substituting amino acids
15   in order to change the function of a protein.

Recombinant human G-CSF mutants have been
prepared, but the method of preparation does not
include overall structure/function relationship
information. For example, the mutation and biochemical
20   modification of Cys 18 has been reported. Kuga et al.,
Biochem. Biophy. Res. Comm 159: 103-111 (1989); Lu et
al., Arch. Biochem. Biophys. 268: 81-92 (1989).

In U.S. Patent No. 4, 810, 643, entitled,
"Production of Pluripotent Granulocyte Colony-
25   Stimulating Factor" (as cited above), polypeptide
analogs and peptide fragments of G-CSF are disclosed
generally. Specific G-CSF analogs disclosed include
those with the cysteins at positions 17, 36, 42, 64, and
74 (of the 174 amino acid species or of those having 175
30   amino acids, the additional amino acid being an
N-terminal methionine) substituted with another amino
acid, (such as serine), and G-CSF with an alanine in the
first (N-terminal) position.

EP 0 335 423 entitled "Modified human G-CSF"
35   reportedly discloses the modification of at least one
amino group in a polypeptide having hG-CSF activity.

- 4 -

EP 0 272 703 entitled "Novel Polypeptide"
reportedly discloses G-CSF derivatives having an amino
acid substituted or deleted at or "in the neighborhood"
of the N terminus.

5   EP 0 459 630, entitled "Polypeptides"
reportedly discloses derivatives of naturally occurring
G-CSF having at least one of the biological properties
of naturally occurring G-CSF and a solution stability of
at least 35% at 5 mg/ml in which the derivative has at

10   least Cys^{17} of the native sequence replaced by a Ser^{17}
residue and Asp^{27} of the native sequence replaced by a
Ser^{27} residue.

EP 0 256 843 entitled "Expression of G-CSF and
Muteins Thereof and Their Uses" reportedly discloses a

15   modified DNA sequence encoding G-CSF wherein the
N-terminus is modified for enhanced expression of
protein in recombinant host cells, without changing the
amino acid sequence of the protein.

EP 0 243 153 entitled "Human G-CSF Protein

20   Expression" reportedly discloses G-CSF to be modified by
inactivating at least one yeast KEX2 protease processing
site for increased yield in recombinant production using
yeast.

Shaw, U.S. Patent No. 4,904,584, entitled

25   "Site-Specific Homogeneous Modification of
Polypeptides," reportedly discloses lysine altered
proteins.

WO/9012874 reportedly discloses cysteine
altered variants of proteins.

30   Australian patent application Document No. AU-
A-10948/92, entitled, "Improved Activation of
Recombinant Proteins" reportedly discloses the addition
of amino acids to either terminus of a G-CSF molecule
for the purpose of aiding in the folding of the molecule

35   after prokaryotic expression.

- 5 -

Australian patent application Document No. AU-
A-76380/91, entitled, "Muteins of the Granulocyte Colony
Stimulating Factor (G-CSF)" reportedly discloses muteins
of the granulocyte stimulating factor G-CSF in the
5   sequence ᴸeu-Gly-His-Ser-Leu-Gly-Ile at position 50-56
of G-CSF with 174 amino acids, and position 53 to 59 of
the G-CSF with 177 amino acids, or/and at least one of
the four histadine residues at positions 43, 79, 156 and
170 of the mature G-CSF with 174 amino acids or at
10   positions 46, 82, 159, or 173 of the mature G-CSF with
177 amino acids.

GB 2 213 821, entitled "Synthetic Human
Granulocyte Colony Stimulating Factor Gene" reportedly
discloses a synthetic G-CSF-encoding nucleic acid
15   sequence incorporating restriction sites to facilitate
the cassette mutagenesis of selected regions, and
flanking restriction sites to facilitate the
incorporation of the gene into a desired expression
system.

20   G-CSF has reportedly been crystallized to some
extent, e.g., EP 344 796, and the overall structure of
G-CSF has been surmised, but only on a gross level.
Bazan, Immunology Today 11: 350-354 (1990); Parry et
al., J. Molecular Recognition 8: 107-110 (1988). To
25   date, there have been no reports of the overall
structure of G-CSF, and no systematic studies of the
relationship of the overall structure and function of
the molecule, studies which are essential to the
systematic design of G-CSF analogs. Accordingly, there
30   exists a need for a method of this systematic design of
G-CSF analogs, and the resultant compositions.

Summary of the Invention

The three dimensional structure of G-CSF has
35   now been determined to the atomic level. From this
three-dimensional structure, one can now forecast with

substantial certainty how changes in the composition of a G-CSF molecule may result in structural changes. These structural characteristics may be correlated with biological activity to design and produce G-CSF analogs.

5   Although others had speculated regarding the three dimensional structure of G-CSF, Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988), these speculations were of no help to those wishing to prepare G-CSF analogs

10   either because the surmised structure was incorrect (Parry et al., supra) and/or because the surmised structure provided no detail correlating the constituent moieties with structure. The present determination of the three-dimensional structure to the atomic level is

15   by far the most complete analysis to date, and provides important information to those wishing to design and prepare G-CSF analogs. For example, from the present three dimensional structural analysis, precise areas of hydrophobicity and hydrophilicity have been determined.

20   Relative hydrophobicity is important because it directly relates to the stability of the molecule. Generally, biological molecules, found in aqueous environments, are externally hydrophilic and internally hydrophobic; in accordance with the second law of

25   thermodynamics provides, this is the lowest energy state and provides for stability. Although one could have speculated that G-CSF's internal core would be hydrophobic, and the outer areas would be hydrophilic, one would have had no way of knowing specific

30   hydrophobic or hydrophilic areas. With the presently provided knowledge of areas of hydrophobicity/-philicity, one may forecast with substantial certainty which changes to the G-CSF molecule will affect the overall structure of the molecule.

35   As a general rule, one may use knowledge of the geography of the hydrophobic and hydrophilic regions

to design analogs in which the overall G-CSF structure is not changed, but change does affect biological activity ("biological activity" being used here in its broadest sense to denote function). One may correlate
5 biological activity to structure. If the structure is not changed, and the mutation has no effect on biological activity, then the mutation has no biological function. If, however, the structure is not changed and the mutation does affect biological activity, then the
10 residue (or atom) is essential to at least one biological function. Some of the present working examples were designed to provide no change in overall structure, yet have a change in biological function.

Based on the correlation of structure to
15 biological activity, one aspect of the present invention relates to G-CSF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the G-CSF amino acid sequence. The modifications may be by addition, substitution, or
20 deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The G-CSF used as a basis
25 for comparison may be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 174 amino acid species of human G-CSF, having an extra N-terminus methionyl residue). The
30 analogs may possess functions different from natural human G-CSF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a
35 decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The

- 8 -

analogs may have no hematopoietic activity, and may
therefore be useful as an antagonist against G-CSF
effect (as, for example, in the overproduction of
G-CSF). From time to time herein the present analogs
5   are referred to as proteins or peptides for convenience,
but contemplated herein are other types of molecules,
such as peptidomimetics or chemically modified peptides.

In another aspect, the present invention
relates to related compositions containing a G-CSF
10 analog as an active ingredient. The term, "related
composition," as used herein, is meant to denote a
composition which may be obtained once the identity of
the G-CSF analog is ascertained (such as a G-CSF analog
labeled with a detectable label, related receptor or
15 pharmaceutical composition). Also considered a related
composition are chemically modified versions of the
G-CSF analog, such as those having attached at least one
polyethylene glycol molecule.

For example, one may prepare a G-CSF analog to
20 which a detectable label is attached, such as a
fluorescent, chemiluminescent or radioactive molecule.
Another example is a pharmaceutical
composition which may be formulated by known techniques
using known materials, see, e.g., Remington's
25 Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing
Co., Easton, Pennsylvania 18042) pages 1435-1712, which
are herein incorporated by reference. Generally, the
formulation will depend on a variety of factors such as
administration, stability, production concerns and other
30 factors. The G-CSF analog may be administered by
injection or by pulmonary administration via inhalation.
Enteric dosage forms may also be available for the
present G-CSF analog compositions, and therefore oral
administration may be effective. G-CSF analogs may be
35 inserted into liposomes or other microcarriers for
delivery, and may be formulated in gels or other

compositions for sustained release. Although preferred
compositions will vary depending on the use to which the
composition will be put, generally, for G-CSF analogs
having at least one of the biological activities of
5   natural G-CSF, preferred pharmaceutical compositions are
those prepared for subcutaneous injection or for
pulmonary administration via inhalation, although the
particular formulations for each type of administration
will depend on the characteristics of the analog.
10   Another example of related composition is a
receptor for the present analog. As used herein, the
term "receptor" indicates a moiety which selectively
binds to the present analog molecule. For example,
antibodies, or fragments thereof, or "recombinant
15   antibodies" (see Huse et al., Science 246:1275 (1989))
may be used as receptors. Selective binding does not
mean only specific binding (although binding-specific
receptors are encompassed herein), but rather that the
binding is not a random event. Receptors may be on the
20   cell surface or intra- or extra-cellular, and may act to
effectuate, inhibit or localize the biological activity
of the present analogs. Receptor binding may also be a
triggering mechanism for a cascade of activity
indirectly related to the analog itself. Also
25   contemplated herein are nucleic acids, vectors
containing such nucleic acids and host cells containing
such nucleic acids which encode such receptors.
                Another example of a related composition is a
G-CSF analog with a chemical moiety attached.
30   Generally, chemical modification may alter biological
activity or antigenicity of a protein, or may alter
other characteristics, and these factors will be taken
into account by a skilled practitioner. As noted above,
one example of such chemical moiety is polyethylene
35   glycol. Modification may include the addition of one or
more hydrophilic or hydrophobic polymer molecules, fatty

- 10 -

acid molecules, or polysaccharide molecules. Examples
of chemical modifiers include polyethylene glycol,
alklpolyethylene glycols, DI-poly(amino acids),
polyvinylpyrrolidone, polyvinyl alcohol, pyran

5   copolymer, acetic acid/acylation, proprionic acid,
palmitic acid, stearic acid, dextran, carboxymethyl
cellulose, pullulan, or agarose. See, Francis, *Focus on
Growth Factors* 3: 4-10 (May 1992)(published by
Mediscript, Mountview Court, Friern Barnet Lane, London

10   N20 OLD, UK). Also, chemical modification may include
an additional protein or portion thereof, use of a
cytotoxic agent, or an antibody. The chemical
modification may also include lecithin.

        In another aspect, the present invention

15   relates to nucleic acids encoding such analogs. The
nucleic acids may be DNAs or RNAs or derivatives
thereof, and will typically be cloned and expressed on a
vector, such as a phage or plasmid containing
appropriate regulatory sequences. The nucleic acids

20   may be labeled (such as using a radioactive,
chemiluminescent, or fluorescent label) for diagnostic
or prognostic purposes, for example. The nucleic acid
sequence may be optimized for expression, such as
including codons preferred for bacterial expression.

25   The nucleic acid and its complementary strand, and
modifications thereof which do not prevent encoooding of
the desired analog are here contemplated.

        In another aspect, the present invention
relates to host cells containing the above nucleic acids

30   encoding the present analogs. Host cells may be
eukaryotic or prokaryotic, and expression systems may
include extra steps relating to the attachment (or
prevention) of sugar groups (glycosylation), proper
folding of the molecule, the addition or deletion of

35   leader sequences or other factors incident to
recombinant expression.

- 11 -

In another aspect the present invention relates to antisense nucleic acids which act to prevent or modify the type or amount of expression of such nucleic acid sequences. These may be prepared by known
5   methods.

In another aspect of the present invention, the nucleic acids encoding a present analog may be used for gene therapy purposes, for example, by placing a vector containing the analog-encoding sequence into a
10   recipient so the nucleic acid itself is expressed inside the recipient who is in need of the analog composition. The vector may first be placed in a carrier, such as a cell, and then the carrier placed into the recipient. Such expression may be localized or systemic. Other
15   carriers include non-naturally occurring carriers, such as liposomes or other microcarriers or particles, which may act to mediate gene transfer into a recipient.

The present invention also provides for computer programs for the expression (such as visual
20   display) of the G-CSF or analog three dimensional structure, and further, a computer program which expresses the identity of each constituent of a G-CSF molecule and the precise location within the overall structure of that constituent, down to the atomic level.
25   Set forth below is one example of such program. There are many currently available computer programs for the expression of the three dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three dimensional
30   structure of a molecule (i.e., for example, a numerical assignment for each atom of a G-CSF molecule along an x, y, and z axis), means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule
35   having such altered coordinates. One may program crystallographic information, i.e., the coordinates of

- 12 -

the location of the atoms of a G-CSF molecule in three
dimension space, wherein such coordinates have been
obtained from crystallographic analysis of said G-CSF
molecule, into such programs to generate a computer
5   program for the expression (such as visual display) of
the G-CSF three dimensional structure. Also provided,
therefore, is a computer program for the expression of
G-CSF analog three dimensional structure. Preferred is
the computer program Insight II, version 4, available
10   from Biosym, San Diego, California, with the coordinates
as set forth in FIGURE 5 input. Preferred expression
means is on a Silicon Graphics 320 VGX computer, with
Crystal Eyes glasses (also available from Silicon
Graphics), which allows one to view the G-CSF molecule
15   or its analog stereoscopically. Alternatively, the
present G-CSF crystallographic coordinates and
diffraction data are also deposited in the Protein Data
Bank, Chemistry Department, Brookhaven National
Laboratory, Upton, New York 119723, USA. One may use
20   these data in preparing a different computer program for
expression of the three dimensional structure of a G-CSF
molecule or analog thereof. Therefore, another aspect
of the present invention is a computer program for the
expression of the three dimensional structure of a G-CSF
25   molecule. Also provided is said computer program for
visual display of the three dimensional structure of a
G-CSF molecule; and further, said program having means
for altering such visual display. Apparatus useful for
expression of such computer program, particularly for
30   the visual display of the computer image of said three
dimensional structure of a G-CSF molecule or analog
thereof is also therefore here provided, as well as
means for preparing said computer program and apparatus.
        The computer program is useful for preparation
35   of G-CSF analogs because one may select specific sites
on the G-CSF molecule for alteration and readily

- 13 -

ascertain the effect the alteration will have on the
overall structure of the G-CSF molecule. Selection of
said site for alteration will depend on the desired
biological characteristic of the G-CSF analog. If one
5   were to randomly change said G-CSF molecule
(r-met-hu-G-CSF) there would be 175^{20} possible
substitutions, and even more analogs having multiple
changes, additions or deletions. By viewing the three
dimensional structure wherein said structure is
10   correlated with the composition of the molecule, the
selection for sites of alteration is no longer a random
event, but sites for alteration may be determined
rationally.

As set forth above, identity of the three
15   dimensional structure of G-CSF, including the placement
of each constituent down to the atomic level has now
yielded information regarding which moieties are
necessary to maintain the overall structure of the G-CSF
molecule. One may therefore select whether to maintain
20   the overall structure of the G-CSF molecule when
preparing a G-CSF analog of the present invention, or
whether (and how) to change the overall structure of the
G-CSF molecule when preparing a G-CSF analog of the
present invention. Optionally, once one has prepared
25   such analog, one may test such analog for a desired
characteristic.

One may, for example, seek to maintain the
overall structure possessed by a non-altered natural or
recombinant G-CSF molecule. The overall structure is
30   presented in Figures 2, 3, and 4, and is described in
more detail below. Maintenance of the overall structure
may ensure receptor binding, a necessary characteristic
for an analog possessing the hematopoietic capabilities
of natural G-CSF (if no receptor binding, signal
35   transduction does not result from the presence of the
analog). It is contemplated that one class of G-CSF

- 14 -

analogs will possess the three dimensional core
structure of a natural or recombinant (non-altered)
G-CSF molecule, yet possess different characteristics,
such as an increased ability to selectively stimulate
5   neutrophils. Another class of G-CSF analogs are those
with a different overall structure which diminishes the
ability of a G-CSF analog molecule to bind to a G-CSF
receptor, and possesses a diminished ability to
selectively stimulate neutrophils as compared to non-
10   altered natural or recombinant G-CSF.

    For example, it is now known which moieties
within the internal regions of the G-CSF molecule are
hydrophobic, and, correspondingly, which moieties on the
external portion of the G-CSF molecule are hydrophilic.
15   Without knowledge of the overall three dimensional
structure, preferably to the atomic level as provided
herein, one could not forecast which alterations within
this hydrophobic internal area would result in a change
in the overall structural conformation of the molecule.
20   An overall structural change could result in a
functional change, such as lack of receptor binding, for
example, and therefore, diminishment of biological
activity as found in non-altered G-CSF. Another class
of G-CSF analogs is therefore G-CSF analogs which
25   possess the same hydrophobicity as (non-altered) natural
or recombinant G-CSF. More particularly, another class
of G-CSF analogs possesses the same hydrophobic moieties
within the four helical bundle of its internal core as
those hydrophobic moieties possessed by (non-altered)
30   natural or recombinant G-CSF yet have a composition
different from said non-altered natural or recombinant
G-CSF.

    Another example relates to external loops
which are structures which connect the internal core
35   (helices) of the G-CSF molecule. From the three
dimensional structure -- including information regarding

- 15 -

the spatial location of the amino acid residues -- one
may forecast that certain changes in certain loops will
not result in overall conformational changes.
Therefore, another class of G-CSF analogs provided
5   herein is that having an altered external loop but
possessing the same overall structure as (non-altered)
natural or recombinant G-CSF. More particularly,
another class of G-CSF analogs provided herein are those
having an altered external loop, said loop being
10   selected from the loop present between helices A and B;
between helices B and C; between helices C and D;
between helices D and A, as those loops and helices are
identified herein. More particularly, said loops,
preferably the AB loop and/or the CD loop are altered to
15   increase the half life of the molecule by stabilizing
said loops. Such stabilization may be by connecting all
or a portion of said loop(s) to a portion of an alpha
helical bundle found in the core of a G-CSF (or analog)
molecule. Such connection may be via beta sheet, salt
20   bridge, disulfide bonds, hydrophobic interaction or
other connecting means available to those skilled in the
art, wherein such connecting means serves to stabilize
said external loop or loops. For example, one may
stabilize the AB or CD loops by connecting the AB loop
25   to one of the helices within the internal region of the
molecule.
         The N-terminus also may be altered without
change in the overall structure of a G-CSF molecule,
because the N-terminus does not effect structural
30   stability of the internal helices, and, although the
external loops are preferred for modification, the same
general statements apply to the N-terminus.
         Additionally, such external loops may be the
site(s) for chemical modification because in (non-
35   altered) natural or recombinant G-CSF such loops are
relatively flexible and tend not to interfere with

- 16 -

receptor binding. Thus, there would be additional room
for a chemical moiety to be directly attached (or
indirectly attached via another chemical moiety which
serves as a chemical connecting means). The chemical
5   moiety may be selected from a variety of moieties
available for modification of one or more function of a
G-CSF molecule. For example, an external loop may
provide sites for the addition of one or more polymer
which serves to increase serum half-life, such as a
10   polyethylene glycol molecule. Such polyethylene glycol
molecule(s) may be added wherein said loop is altered to
include additional lysines which have reactive side
groups to which polyethylene glycol moieties are capable
of attaching. Other classes of chemical moieties may
15   also be attached to one or more external loops,
including but not limited to other biologically active
molecules, such as receptors, other therapeutic proteins
(such as other hematopoietic factors which would
engender a hybrid molecule), or cytotoxic agents (such
20   as diphtheria toxin). This list is of course not
complete; one skilled in the art possessed of the
desired chemical moiety will have the means to effect
attachment of said desired moiety to the desired
external loop. Therefore, another class of the present
25   G-CSF analogs includes those with at least one
alteration in an external loop wherein said alteration
provides for the addition of a chemical moiety such as
at least one polyethylene glycol molecule.
          Deletions, such as deletions of sites
30   recognized by proteins for degradation of the molecule,
may also be effectual in the external loops. This
provides alternative means for increasing half-life of a
molecule otherwise having the G-CSF receptor binding and
signal transduction capabilities (i.e., the ability to
35   selectively stimulate the maturation of neutrophils).
Therefore, another class of the present G-CSF analogs

- 17 -

includes those with at least one alteration in an
external loop wherein said alteration decreases the
turnover of said analog by proteases. Preferred loops
for such alterations are the AB loop and the CD loop.

5   One may prepare an abbreviated G-CSF molecule by
deleting a portion of the amino acid residues found in
the external loops (identified in more detail below),
said abbreviated G-CSF molecule may have additional
advantages in preparation or in biological function.

10   Another example relates to the relative
charges between amino acid residues which are in
proximity to each other. As noted above, the G-CSF
molecule contains a relatively tightly packed four
helical bundle. Some of the faces on the helices face

15   other helices. At the point (such as a residue) where a
helix faces another helix, the two amino acid moieties
which face each other may have the same charge, and thus
tend to repel each other, which lends instability to the
overall molecule. This may be eliminated by changing

20   the charge (to an opposite charge or a neutral charge)
of one or both of the amino acid moieties so that there
is no repelling. Therefore, another class of G-CSF
analogs includes those G-CSF analogs having been altered
to modify instability due to surface interactions, such

25   as electron charge location.

          In another aspect, the present invention
relates to methods for designing G-CSF analogs and
related compositions and the products of those methods.
The end products of the methods may be the G-CSF analogs

30   as defined above or related compositions. For instance,
the examples disclosed herein demonstrate (a) the
effects of changes in the constituents (i.e., chemical
moieties) of the G-CSF molecule on the G-CSF structure
and (b) the effects of changes in structure on

35   biological function. Essentially, therefore, another

- 18 -

aspect of the present invention is a method for
preparing a G-CSF analog comprising the steps of:

        (a)   viewing information conveying the three
dimensional structure of a G-CSF molecule wherein the
5   chemical moieties, such as each amino acid residue or
each atom of each amino acid residue, of the G-CSF
molecule are correlated with said structure;

        (b)   selecting from said information a site on
a G-CSF molecule for alteration;

10   (c)   preparing a G-CSF analog molecule having
such alteration; and

        (d)   optionally, testing such G-CSF analog
molecule for a desired characteristic.

        One may use the here provided computer
15   programs for a computer-based method for preparing a
G-CSF analog. Another aspect of the present invention
is therefore a computer based method for preparing a
G-CSF analog comprising the steps of:

        (a)   providing computer expression of the
20   three dimensional structure of a G-CSF molecule wherein
the chemical moieties, such as each amino acid residue
or each atom of each amino acid residue, of the G-CSF
molecule are correlated with said structure;

        (b)   selecting from said computer expression a
25   site on a G-CSF molecule for alteration;

        (c)   preparing a G-CSF molecule having such
alteration; and

        (d)   optionally, testing such G-CSF molecule
for a desired characteristic.

30   More specifically, the present invention
provides a method for preparing a G-CSF analog
comprising the steps of:

        (a)   viewing the three dimensional structure
of a G-CSF molecule via a computer, said computer
35   programmed (i) to express the coordinates of a G-CSF
molecule in three dimensional space, and (ii) to allow

- 19 -

for entry of information for alteration of said G-CSF
expression and viewing thereof;

      (b)   selecting a site on said visual image of
said G-CSF molecule for alteration;

5   (c)   entering information for said alteration
on said computer;

      (d)   viewing a three dimensional structure of
said altered G-CSF molecule via said computer;

      (e)   optionally repeating steps (a)-(e);

10   (f)   preparing a G-CSF analog with said
alteration; and

      (g)   optionally testing said G-CSF analog for a
desired characteristic.

      In another aspect, the present invention
15   relates to methods of using the present G-CSF analogs
and related compositions and methods for the treatment
or protection of mammals, either alone or in combination
with other hematopoietic factors or drugs in the
treatment of hematopoietic disorders. It is
20   contemplated that one aspect of designing G-CSF analogs
will be the goal of enhancing or modifying the
characteristics non-modified G-CSF is known to have.

      For example, the present analogs may possess
enhanced or modified activities, so, where G-CSF is
25   useful in the treatment of (for example) neutropenia,
the present compositions and methods may also be of such
use.

      Another example is the modification of G-CSF
for the purpose of interacting more effectively when
30   used in combination with other factors particularly in
the treatment of hematopoietic disorders. One example
of such combination use is to use an early-acting
hematopoietic factor (i.e., a factor which acts earlier
in the hematopoiesis cascade on relatively
35   undifferentiated cells) and either simultaneously or in
seriatim use of a later-acting hematopoietic factor,

- 20 -

such as G-CSF or analog thereof (as G-CSF acts on the
CFU-GM lineage in the selective stimulation of
neutrophils). The present methods and compositions may
be useful in therapy involving such combinations or
5   "cocktails" of hematopoietic factors.

The present compositions and methods may also
be useful in the treatment of leukopenia, mylogenous
leukemia, severe chronic neutropenia, aplastic anemia,
glycogen storage disease, mucosistitis, and other bone
10   marrow failure states. The present compositions and
methods may also be useful in the treatment of
hematopoietic deficits arising from chemotherapy or from
radiation therapy. The success of bone marrow
transplantation, or the use of peripheral blood
15   progenitor cells for transplantation, for example, may
be enhanced by application of the present compositions
(proteins or nucleic acids for gene therapy) and
methods. The present compositions and methods may also
be useful in the treatment of infectious diseases, such
20   in the context of wound healing, burn treatment,
bacteremia, septicemia, fungal infections, endocarditis,
osteopyelitis, infection related to abdominal trauma,
infections not responding to antibiotics, pneumonia and
the treatment of bacterial inflammation may also benefit
25   from the application of the present compositions and
methods. In addition, the present compositions and
methods may be useful in the treatment of leukemia based
upon a reported ability to differentiate leukemic cells.
Welte et al., PNAS-USA 82: 1526-1530 (1985). Other
30   applications include the treatment of individuals with
tumors, using the present compositions and methods,
optionally in the presence of receptors (such as
antibodies) which bind to the tumor cells. For review
articles on therapeutic applications, see Lieshhke and
35   Burgess, N.Engl.J.Med. 327: 28-34 and 99-106 (1992) both
of which are herein incorporated by reference.

- 21 -

The present compositions and methods may also
be useful to act as intermediaries in the production of
other moieties; for example, G-CSF has been reported to
influence the production of other hematopoietic factors
5   and this function (if ascertained) may be enhanced or
modified via the present compositions and/or methods.

The compositions related to the present G-CSF
analogs, such as receptors, may be useful to act as an
antagonist which prevents the activity of G-CSF or an
10   analog. One may obtain a composition with some or all
of the activity of non-altered G-CSF or a G-CSF analog,
and add one or more chemical moieties to alter one or
more properties of such G-CSF or analog. With knowledge
of the three dimensional conformation, one may forecast
15   the best geographic location for such chemical
modification to achieve the desired effect.

General objectives in chemical modification
may include improved half-life (such as reduced renal,
immunological or cellular clearance), altered
20   bioactivity (such as altered enzymatic properties,
dissociated bioactivities or activity in organic
solvents), reduced toxicity (such as concealing toxic
epitopes, compartmentalization, and selective
biodistribution), altered immunoreactivity (reduced
25   immunogenicity, reduced antigenicity or adjuvant
action), or altered physical properties (such as
increased solubility, improved thermal stability,
improved mechanical stability, or conformational
stabilization). See Francis, *Focus on Growth Factors* 3:
30   4-10 (May 1992)(published by Mediscript, Mountview
Court, Friern Barnet Lane, London N20 OLD, UK).

The examples below are illustrative of the
present invention and are not intended as a limitation.
It is understood that variations and modifications will
35   occur to those skilled in the art, and it is intended
that the appended claims cover all such equivalent

- 22 -

variations which come within the scope of the invention
as claimed.

Detailed Description of the Drawings

5   FIGURE 1 is an illustration of the amino acid
sequence of the 174 amino acid species of G-CSF with an
additional N-terminal methionine (Seq. ID No.: 1) (Seq.
ID No.: 2).

           FIGURE 2 is an topology diagram of the
10   crystalline structure of G-CSF, as well as hGH, pGH,
GM-CSF, INF-B, IL-2, and IL-4. These illustrations are
based on inspection of cited references. The length of
secondary structural elements are drawn in proportion to
the number of residues. A, B, C, and D helices are
15   labeled according to the scheme used herein for G-CSF.
For INF-ß, the original labeling of helices is indicated
in parentheses.

           FIGURE 3 is an "ribbon diagram" of the three
dimensional structure of G-CSF. Helix A is amino acid
20   residues 11-39 (numbered according to Figure 1, above),
helix B is amino acid residues 72-91, helix C is amino
acid residues 100-123, and helix D is amino acid
residues 143-173. The relatively short 3^{10} helix is at
amino acid residues 45-48, and the alpha helix is at
25   amino acid residues 48-53. Residues 93-95 form almost
one turn of a left handed helix.

           FIGURE 4 is a "barrel diagram" of the three
dimensional structure of G-CSF. Shown in various shades
of gray are the overall cylinders and their orientations
30   for the three dimensional structure of G-CSF. The
numbers indicate amino acid residue position according
to FIGURE 1 above.

           FIGURE 5 is a list of the coordinates used to
generate a computer-aided visual image of the three-
35   dimensional structure of G-CSF. The coordinates are set
forth below. The columns correspond to separate field:

- 23 -

     (i)   Field 1 (from the left hand side) is the atom,

     (ii)   Field 2 is the assigned atom number,

     (iii)   Field 3 is the atom name (according to
5 the periodic table standard nomenclature, with CB being
carbon atom Beta, CG is Carbon atom Gamma, etc.);

     (iv)   Field 4 is the residue type (according
to three letter nomenclature for amino acids as found
in, e.g., Stryer, Biochemistry, 3d Ed., W.H. Freeman and
10 Company, N.Y. 1988, inside back cover);

     (v)   Fields 5-7 are the x-axis, y-axis and
z-axis positions of the atom;

     (vi)   Field 8 (often a "1.00") designates
occupancy at that position;
15   (vii)   Field 9 designates the B-factor;

     (viii)   Field 10 designates the molecule
designation. Three molecules (designated a, b, and c)
of G-CSF crystallized together as a unit. The
designation a, b, or c indicates which coordinates are
20 from which molecule. The number after the letter (1, 2,
or 3) indicates the assigned amino acid residue
position, with molecule A having assigned positions 10-
175, molecule B having assigned positions 210-375, and
molecule C having assigned positions 410-575. These
25 positions were so designated so that there would be no
overlap among the three molecules which crystallized
together. (The "W" designation indicates water).

     FIGURE 6 is a schematic representation of the
strategy involved in refining the crystallization matrix
30 for parameters involved in crystallization. The
crystallization matrix corresponds to the final
concentration of the components (salts, buffers and
precipitants) of the crystallization solutions in the
wells of a 24 well tissue culture plate. These
35 concentrations are produced by pipetting the appropriate
volume of stock solutions into the wells of the

- 24 -

microtiter plate. To design the matrix, the
crystallographer decides on an upper and lower
concentration of the component. These upper and lower
concentrations can be pipetted along either the rows
5   (e.g., A1-A6, B1-B6, C1-C6 or D1-D6) or along the entire
tray (A1-D6). The former method is useful for checking
reproducibility of crystal growth of a single component
along a limited number of wells, whereas the later
method is more useful in initial screening. The results
10   of several stages of refinement of the crystallization
matrix are illustrated by a representation of three
plates. The increase in shading in the wells indicates
a positive crystallization result which, in the final
stages, would be X-ray quality crystals but in the
15   initial stages could be oil droplets, granular
precipitates or small crystals approximately less than
0.05 mm in size. Part A represents an initial screen of
one parameter in which the range of concentration
between the first well (A1) and last well (D6) is large
20   and the concentration increase between wells is
calculated as ((concentration A1)-(concentration
D6))/23). Part B represents that in later stages of the
crystallization matrix refinement of the concentration
spread between A1 and D6 would be reduced which would
25   result in more crystals formed per plate. Part C
indicates a final stage of matrix refinement in which
quality crystals are found in most wells of the plate.

Detailed Description of the Invention

30   The present invention grows out of the
discovery of the three dimensional structure of G-CSF.
This three dimensional structure has been expressed via
computer program for stereoscopic viewing. By viewing
this stereoscopically, structure-function relationships
35   identified and G-CSF analogs have been designed and
made.

- 25 -

The Overall Three Dimensional Structure of G-CSF

The G-CSF used to ascertain the structure was a non-glycosylated 174 amino acid species having an
5   extra N-terminal methionine residue incident to bacterial expression. The DNA and amino acid sequence of this G-CSF are illustrated in FIGURE 1.

Overall, the three dimensional structure of G-CSF is predominantly helical, with 103 of the 175
10   residues forming a 4-alpha-helical bundle. The only other secondary structure is found in the loop between the first two long helices where a 4 residue 3^{10} helix is immediately followed by a 6 residue alpha helix. As shown in FIGURE 2, the overall structure has been
15   compared with the structure reported for other proteins: growth hormone (Abdel-Meguid et al., PNAS-USA 84: 6434 (1987) and Vos et al., Science 255: 305-312 (1992)), granulocyte macrophage colony stimulating factor (Diederichs et al., Science 254: 1779-1782 (1991),
20   interferon-ß (Senda et al., EMBO J. 11: 3193-3201 (1992)), interleukin-2 (McKay Science 257: 1673-1677 (1992)) and interleukin-4 (Powers et al., Science 256: 1673-1677 (1992), and Smith et al., J. Mol. Biol. 224: 899-904 (1992)). Structural similarity among these
25   growth factors occurs despite the absence of similarity in their amino acid sequences.

Presently, the structural information was correlation of G-CSF biochemistry, and this can be

- 26 -

summarized as follows (with sequence position 1 being at the N-terminus):

Sequence Position	Description of Structure	Analysis
1-10	Extended chain	Deletion causes no loss of biological activity
Cys 18	Partially buried	Reactive with DTNB and Thimersososl but not with iodo-acetate
34	Alternative splice site	Insertion reduces biological activity
20-47 (inclusive)	Helix A, first disulfide and portion of AB helix	Predicted receptor binding region based on neutralizing antibody data
20, 23, 24	Helix A	Single alanine mutation of residue(s) reduces biological activity. Predicted receptor binding (Site B).
165-175 (inclusive)	Carboxy terminus	Deletion reduces biological activity

This biochemical information, having been gleaned from antibody binding studies, see Layton et al., Biochemistry 266: 23815-23823 (1991), was superimposed on the three-dimensional structure in order to design G-CSF analogs. The design, preparation, and testing of these G-CSF analogs is described in Example 1 below.

EXAMPLE 1

This Example describes the preparation of crystalline G-CSF, the visualization of the three dimensional structure of recombinant human G-CSF via

- 27 -

computer-generated image, the preparation of analogs, using site-directed mutagenesis or nucleic acid amplification methods, the biological assays and HPLC analysis used to analyze the G-CSF analogs, and the

5   resulting determination of overall structure/function relationships. All cited publications are herein incorporated by reference.

A.   Use of Automated Crystallization

10   The need for a three-dimensional structure of recombinant human granulocyte colony stimulating factor (r-hu-G-CSF), and the availability of large quantities of the purified protein, led to methods of crystal growth by incomplete factorial sampling and seeding.

15   Starting with the implementation of incomplete factorial crystallization described by Jancarik and Kim, J. Appl. Crystallogr. 24: 409 (1991) solution conditions that yielded oil droplets and birefringence aggregates were ascertained. Also, software and hardware of an

20   automated pipetting system were modified to produce some 400 different crystallization conditions per day. Weber, J. Appl. Crystallogr. 20: 366-373 (1987). This procedure led to a crystallization solution which produced r-hu-G-CSF crystals.

25   The size, reproducibility and quality of the crystals was improved by a seeding method in which the number of "nucleation initiating units" was estimated by serial dilution of a seeding solution. These methods yielded reproducible growth of 2.0 mm r-hu-G-CSF

30   crystals. The space group of these crystals is $P2_12_12_1$ with cell dimensions of a=90 Å, b=110 Å and c=49 Å, and they diffract to a resolution of 2.0 Å.

1.   Overall Methodology

To search for the crystallizing conditions of

35   a new protein, Carter and Carter, J. Biol. Chem. 254:

- 28 -

122219-12223 (1979) proposed the incomplete factorial
method. They suggested that a sampling of a large
number of randomly selected, but generally probable,
crystallizing conditions may lead to a successful

5   combination of reagents that produce protein
crystallization. This idea was implemented by Jancarik
and Kim, J. Appl. Crystallogr. 24: 409(1991), who
described 32 solutions for the initial crystallization
trials which cover a range of pH, salts and

10   precipitants. Here we describe an extension of their
implementation to an expanded set of 70 solutions. To
minimize the human effort and error of solution
preparation, the method has been programmed for an
automatic pipetting machine.

15   Following Weber's method of successive
automated grid searching (SAGS), J.Cryst. Growth 90:
318-324(1988), the robotic system was used to generate a
series of solutions which continually refined the
crystallization conditions of temperature, pH, salts and

20   precipitant. Once a solution that could reproducibly
grow crystals was determined, a seeding technique which
greatly improved the quality of the crystals was
developed. When these methods were combined, hundreds
of diffraction quality crystals (crystals diffracting to

25   at least about 2.5 Angstroms, preferably having at least
portions diffracting to below 2 Angstroms, and more
preferably, approximately 1 Angstrom) were produced in a
few days.

                Generally, the method for crystallization,

30   which may be used with any protein one desires to
crystallize, comprises the steps of:

                (a) combining aqueous aliquots of the desired
protein with either (i) aliquots of a salt solution,
each aliquot having a different concentration of salt;

35   or (ii) aliquots of a precipitant solution, each aliquot
having a different concentration of precipitant,

- 29 -

optionally wherein each combined aliquot is combined in
the presence of a range of pH;

(b)   observing said combined aliquots for
precrystalline formations, and selecting said salt or
5   precipitant combination and said pH which is efficacious
in producing precrystalline forms, or, if no
precrystalline forms are so produced, increasing the
protein starting concentration of said aqueous aliquots
of protein;

10   (c)   after said salt or said precipitant
concentration is selected, repeating step (a) with said
previously unselected solution in the presence of said
selected concentration; and

(d)   repeating step (b) and step (a) until a
15   crystal of desired quality is obtained.

The above method may optionally be automated,
which provides vast savings in time and labor.
Preferred protein starting concentrations are between
10mg/ml and 20mg/ml, however this starting concentration
20   will vary with the protein (the G-CSF below was analyzed
using 33mg/ml). A preferred range of salt solution to
begin analysis with is (NaCl) of 0-2.5M. A preferred
precipitant is polyethylene glycol 8000, however, other
precipitants include organic solvents (such as ethanol),
25   polyethylene glycol molecules having a molecular weight
in the range of 500-20,000, and other precipitants known
to those skilled in the art. The preferred pH range is
pH 4.5 , 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and
9.0. Precrystallization forms include oils,
30   birefringement precipitants, small crystals
(< approximately 0.05 mm), medium crystals
(approximately 0.5 to .5 mm) and large crystals
(> approximately 0.5 mm). The preferred time for
waiting to see a crystalline structure is 48 hours,
35   although weekly observation is also preferred, and
generally, after about one month, a different protein

- 30 -

concentration is utilized (generally the protein
concentration is increased). Automation is preferred,
using the Accuflex system as modified. The preferred
automation parameters are described below.

5   Generally, protein with a concentration
between 10 mg/ml and 20 mg/ml was combined with a range
of NaCl solutions from 0-2.5 M, and each such
combination was performed (separately) in the presence
of the above range of concentrations. Once a

10   precrystallization structure is observed, that salt
concentration and pH range are optimized in a separate
experiment, until the desired crystal quality is
achieved. Next, the precipitant concentration, in the
presence of varying levels of pH is also optimized.

15   When both are optimized, the optimal conditions are
performed at once to achieve the desired result (this is
diagrammed in FIGURE 6).

          a.   Implementation of an automated
pipetting system

20   Drops and reservoir solutions were prepared by
an Accuflex pipetting system (ICN Pharmaceuticals, Costa
Mesa, CA) which is controlled by a personal computer
that sends ASCII codes through a standard serial
interface. The pipetter samples six different solutions

25   by means of a rotating valve and pipettes these
solutions onto a plate whose translation in a x-y
coordinate system can be controlled. The vertical
component of the system manipulates a syringe that is
capable both of dispensing and retrieving liquid.

30   The software provided with the Accuflex was
based on the SAGS method as proposed by Cox and Weber,
J.Appl. Crystallogr. 20: 366-373 (1987). This method
involves the systematic variation of two major
crystallization parameters, pH and precipitant

35   concentration, with provision to vary two others. While

building on these concepts, the software used here
provided greater flexibility in the design and
implementation of the crystallization solutions used in
the automated grid searching strategy. As a result of
5 this flexibility the present software also created a
larger number of different solutions. This is essential
for the implementation of the incomplete factorial
method as described in that section below.

To improve the speed and design of the
10 automated grid searching strategy, the Accuflex
pipetting system required software and hardware
modifications. The hardware changes allowed the use of
two different micro-titer trays, one used for handing
drop and one used for sitting drop experiments, and a
15 Plexiglas tray which held 24 additional buffer, salt and
precipitant solutions. These additional solutions
expanded the grid of crystallizing conditions that could
be surveyed.

To utilize the hardware modifications, the
20 pipetting software was written in two subroutines; one
subroutine allows the crystallographer to design a
matrix of crystallization solutions based on the
concentrations of their components and the second
subroutine to translate these concentrations into the
25 computer code which pipettes the proper volumes of the
solutions into the crystallization trays. The
concentration matrices can be generated by either of two
programs. The first program (MRF, available from Amgen,
Inc., Thousand Oaks, CA) refers to a list of stock
30 solution concentrations supplied by the crystallographer
and calculates the required volume to be pipette to
achieve the designated concentration. The second
method, which is preferred, incorporates a spread sheet
program (Lotus) which can be used to make more
35 sophisticated gradients of precipitants or pH. The
concentration matrix created by either program is

- 32 -

interpreted by the control program (SUX, a modification
of the program found in the Accuflex pipetter originally
and available from Amgen, Inc., Thousand Oaks, CA) and
the wells are filled accordingly.

5   b.   Implementation of the Incomplete
Factorial Method

              The convenience of the modified pipetting
system for preparing diverse solutions improved the
implementation of an expanded incomplete factorial
10   method.   The development of a new set of crystallization
solutions having "random" components was generated using
the program INFAC, Carter et al., J.Cryst. Growth 90:
·60-73(1988) which produced a list containing 96 random
combinations of one factor from three variables.
15   Combinations of calcium and phosphate which immediately
precipitated were eliminated, leaving 70 distinct
combinations of precipitants, salts and buffers.   These
combinations were prepared using the automated pipetter
and incubated for 1 week.   The mixtures were inspected
20   and solutions which formed precipitants were prepared
again with lower concentrations of their components.
This was repeated until all wells were clear of
precipitant.

                          c.   Crystallization of r-hu-G-CSF
25   Several different crystallization strategies
were used to find a solution which produced x-ray
quality crystals.   These strategies included the use of
the incomplete factorial method, refinement of the
crystallization conditions using successive automated
30   grid searches (SAGS), implementation of a seeding
technique and development of a crystal production
procedure which yielded hundreds of quality crystals
overnight.   Unless otherwise noted the screening and
production of r-hu-G-CSF crystals utilized the hanging
35   drop vapor diffusion method. Afinsen et al., Physical

- 33 -

principles of protein crystallization. In: Eisenberg
(ed.), Advances in Protein Chemistry 41: 1-33 (1991).

5   The initial screening for crystallization
conditions of r-hu-G-CSF used the Jancarik and Kim,
J.Appl.Crystallogr. 24: 409(1991) incomplete factorial
method which resulted in several solutions that produced
"precrystallization" results. These results included
birefringent precipitants, oils and very small crystals
(< .05 mm). These precrystallizations solutions then
10   served as the starting points for systematic screening.

The screening process required the development
of crystallization matrices. These matrices
corresponded to the concentration of the components in
the crystallization solutions and were created using the
15   IBM-PC based spread sheet Lotus™ and implemented with
the modified Accuflex pipetting system. The strategy in
designing the matrices was to vary one crystallization
condition (such as salt concentration) while holding the
other conditions such as pH, and precipitant
20   concentration constant. At the start of screening, the
concentration range of the varied condition was large
but the concentration was successively refined until all
wells in the micro-titer tray produced the same
crystallization result. These results were scored as
25   follows: crystals, birefringement precipitate, granular
precipitate, oil droplets and amorphous mass. If the
concentration of a crystallization parameter did not
produce at least a precipitant, the concentration of
that parameter was increased until a precipitant formed.
30   After each tray was produced, it was left undisturbed
for at least two days and then inspected for crystal
growth. After this initial screening, the trays were
then inspected on a weekly basis.

From this screening process, two independent
35   solutions with the same pH and precipitant but differing
in salts (MgCl, LiSO$_4$) were identified which produced

- 34 -

small (0.1 x 0.05 x 0.05 mm) crystals. Based on these results, a new series of concentration matrices were produced which varied MgCl with respect to $LiSO_4$ while keeping the other crystallization parameters constant.

5   This series of experiments resulted in identification of a solution which produced diffraction quality crystals (> approximately 0.5 mm) in about three weeks. To find this crystallization growth solution (100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM LiSO4 and 8% PEG 8k) approximately

10   8,000 conditions had been screened which consumed about 300 mg of protein.

        The size of the crystals depended on the number of crystals forming per drop. Typically 3 to 5 crystals would be formed with average size of (1.0 x 0.7

15   x 0.7 mm). Two morphologies which had an identical space group ($P2_12_12_1$) and unit cell dimensions a=90.2, b=110.2, c=49.5 were obtained depending on whether or not seeding (see below) was implemented. Without seeding, the r-hu-G-CSF crystals had one long flat

20   surface and rounded edges.

        When seeding was employed, crystals with sharp faces were observed in the drop within 4 to 6 hours (0.05 by 0.05 by 0.05 mm). Within 24 hours, crystals had grown to (0.7 by 0.7 by 0.7 mm) and continued to

25   grow beyond 2 mm depending on the number of crystals forming in the drop.

        d.   Seeding and determination of nucleation initiation sites.

        The presently provided method for seeding

30   crystals establishes the number of nucleation initiation units in each individual well used (here, after the optimum conditions for growing crystals had been determined). The method here is advantageous in that the number of "seeds" affects the quality of the

35   crystals, and this in turn affects the degree of resolution. The present seeding here also provides

- 35 -

advantages in that with seeding, G-CSF crystal grows in
a period of about 3 days, whereas without seeding, the
growth takes approximately three weeks.

In one series of production growth (see
5   methods), showers of small but well defined crystals
were produced overnight (<0.01 x 0.01 x0.01 mm).
Crystallization conditions were followed as described
above except that a pipette tip employed in previously
had been reused. Presumably, the crystal showering
10   effect was caused by small nucleation units which had
formed in the used tip and which provided sites of
nucleation for the crystals. Addition of a small amount
(0.5 ul) of the drops containing the crystal showers to
a new drop under standard production growth conditions
15   resulted in a shower of crystals overnight. This method
was used to produce several trays of drops containing
crystal showers which we termed "seed stock".

The number of nucleation initiation units
(NIU) contained within the "seed stock" drops was
20   estimated to attempt to improve the reproducibility and
quality of the r-hu-GCSF crystals. To determine the
number of NIU in the "seed stock", an aliquot of the
drop was serially diluted along a 96 well microtiter
plate. The microtiter plate was prepared by adding 50
25   ul of a solution containing equal volumes of r-hu-G-CSF
(33 mg/ml) and the crystal growth solution (described
above) in each well. An aliquot (3 ul) of one of the
"seed stock" drops was transferred to the first well of
the microtiter plate. The solution in the well was
30   mixed and 3 ul was then transferred to the next well
along the row of the microtiter plate. Each row of the
microtiter plate was similarly prepared and the tray was
sealed with plastic tape. Overnight, small crystals
formed in the bottom of the wells of the microtiter
35   plate and the number of crystals in the wells were
correlated to the dilution of the original "seed stock".

- 36 -

To produce large single crystals, the "seed stock" drop
was appropriately diluted into fresh CGS and then an
aliquot of this solution containing the NIU was
transferred to a drop

5   Once crystallization conditions had been
optimized, crystals were grown in a production method in
which 3 ml each of CGS and r-hu-G-CSF (33 mg/ml) were
mixed to create 5 trays (each having 24 wells). This
method included the production of the refined

10 crystallization solution in liter quantities, mixing
this solution with protein and placing the
protein/crystallization solution in either hanging drop
or sitting drop trays. This process typically yielded
100 to 300 quality crystals (>0.5 mm) in about 5 days.

15   e. Experimental Methods
          Materials

          Crystallographic information was obtained
starting with r-hu-met-G-CSF with the amino acid
sequence as provided in FIGURE 1 with a specific

20 activity of 1.0 +/- 0.6 x 10^8U/mg (as measured by cell
mitogenesis assay in a 10 mM acetate buffer at pH 4.0
(in Water for Injection) at a concentration of
approximately 3 mg/ml solution was concentrated with an
Amicon concentrator at 75 psi using a YM10 filter. The

25 solution was typically concentrated 10 fold at 4°C and
stored for several months.
          Initial Screening

          Crystals suitable for X-ray analysis were
obtained by vapor-diffusion equilibrium using hanging

30 drops. For preliminary screening, 7 ul of the protein
solution at 33 mg/ml (as prepared above) was mixed with
an equal volume of the well solution, placed on
siliconized glass plates and suspended over the well
solution utilizing Linbro tissue culture plates (Flow

35 Laboratories, McLean, Va). All of the pipetting was
performed with the Accuflex pipetter, however, trays

were removed from the automated pipetter after the well
solutions had been created and thoroughly mixed for at
least 10 minutes with a table top shaker. The Linbro
trays were then returned to the pipetter which added the
5 well and protein solutions to the siliconized cover
slips. The cover slips were then inverted and sealed
over 1 ml of the well solutions with silicon grease.
The components of the automated
crystallization system are as follows. A PC-DOS
10 computer system was used to design a matrix of
crystallization solutions based on the concentration of
their components. These matrices were produced with
either MRF of the Lotus spread sheet (described above).
The final product of these programs is a data file.
15 This file contains the information required by the SUX
program to pipette the appropriate volume of the stock
solutions to obtain the concentrations described in the
matrices. The SUX program information was passed
through a serial I/O port and used to dictate to the
20 Accuflex pipetting system the position of the valve
relative to the stock solutions, the amount of solution
to be retrieved, and then pipetted into the wells of the
microtiter plates and the X-Y position of each well (the
column/row of each well). Addition information was
25 transmitted to the pipetter which included the Z
position (height) of the syringe during filling as well
as the position of a drain where the system pauses to
purge the syringe between fillings of different
solutions. The 24 well microtiter plate (either Linbro
30 or Cryschem) and cover slip holder was placed on a plate
which was moved in the X-Y plane. Movement of the plate
allowed the pipetter to position the syringe to pipette
into the wells. It also positioned the coverslips and
vials and extract solutions from these sources. Prior
35 the pipetting, the Linbro microtiter plates had a thin
film of grease applied around the edges of the wells.

- 38 -

After the crystallization solutions were prepared in the
wells and before they were transferred to the cover
slips, the microtiter plate was removed from the
pipetting system, and solutions were allowed to mix on a
5   table top shaker for ten minutes. After mixing, the
well solution was either transferred to the cover slips
(in the case of the hanging drop protocol) or
transferred to the middle post in the well (in the case
of the sitting drop protocol). Protein was extracted
10   from a vial and added to the coverslip drop containing
the well solution (or to the post). Plastic tape was
applied to the top of the Cryschem plate to seal the
wells.

       Production Growth

15   Once conditions for crystallization had been
optimized, crystal growth was performed utilizing a
"production" method. The crystallization solution which
contained 100 mM Mes pH 5.8, 380 mM MgCl2, 220 mM LiSO4,
and 8% PEG 8K was made in 1 liter quantities. Utilizing
20   an Eppindorf syringe pipetter, 1 ml aliquots of this
solution were pipetted into each of the wells of the
Linbro plate. A solution containing 50% of this
solution and 50% G-CSF (33 mg/ml) was mixed and pipetted
onto the siliconized cover slips. Typical volumes of
25   these drops were between 50 and 100 ul and because of
the large size of these drops, great care was taken in
flipping the coverslips and suspending the drops over
the wells.

       Data Collection

30   The structure has been refined with X-PLOR
(Bruniger, X-PLOR version 3.0, A system for
crystallography and NMR, Yale University, New Haven CT)
against 2.2Å data collected on an R-AXIS (Molecular
Structure, Corp. Houston, TX) imaging plate detector.

35

- 39 -

f.   Observations

As an effective recombinant human therapeutic,
r-hu-G-CSF has been produced in large quantities and
gram levels have been made available for structural
5   analysis. The crystallization methods provided herein
are likely to find other applications as other proteins
of interest become available. This method can be
applied to any crystallographic project which has large
quantities of protein (approximately >200 mg). As one
10   skilled in the art will recognize, the present materials
and methods may be modified and equivalent materials and
methods may be available for crystallization of other
proteins.

B.   Computer Program For Visualizing The
15   Three Dimensional Structure of G-CSF

Although diagrams, such as those in the
Figures herein, are useful for visualizing the three
dimensional structure of G-CSF, a computer program which
allows for stereoscopic viewing of the molecule is
20   contemplated as preferred. This stereoscopic viewing,
or "virtual reality" as those in the art sometimes refer
to it, allows one to visualize the structure in its
three dimensional form from every angle in a wide range
of resolution, from macromolecular structure down to the
25   atomic level. The computer programs contemplated herein
also allow one to change perspective of the viewing
angle of the molecule, for example by rotating the
molecule. The contemplated programs also respond to
changes so that one may, for example, delete, add, or
30   substitute one or more images of atoms, including entire
amino acid residues, or add chemical moieties to
existing or substituted groups, and visualize the change
in structure.

Other computer based systems may be used; the
35   elements being: (a) a means for entering information,
such as orthogonal coordinates or other numerically

- 40 -

assigned coordinates of the three dimensional structure
of G-CSF; (b) a means for expressing such coordinates,
such as visual means so that one may view the three
dimensional structure and correlate such three
5   dimensional structure with the composition of the G-CSF
molecule, such as the amino acid composition; (c)
optionally, means for entering information which alters
the composition of the G-CSF molecule expressed, so that
the image of such three dimensional structure displays
10   the altered composition.

        The coordinates for the preferred computer
program used are presented in FIGURE 5. The preferred
computer program is Insight II, version 4, available
from Biosym in San Diego, CA. For the raw
15   crystallographic structure, the observed intensities of
the diffraction data ("F-obs") and the orthogonal
coordinates are also deposited in the Protein Data Bank,
Chemistry Department, Brookhaven National Laboratory,
Upton, New York 119723, USA and these are herein
20   incorporated by reference.

        Once the coordinates are entered into the
Insight II program, one can easily display the three
dimensional G-CSF molecule representation on a computer
screen. The preferred computer system for display is
25   Silicon Graphics 320 VGX (San Diego, CA). For
stereoscopic viewing, one may wear eyewear (Crystal
Eyes, Silicon Graphics) which allows one to visualize
the G-CSF molecule in three dimensions stereoscopically,
so one may turn the molecule and envision molecular
30   design.

        Thus, the present invention provides a method
of designing or preparing a G-CSF analog with the aid of
a computer comprising:

        (a)   providing said computer with the means for
35   displaying the three dimensional structure of a G-CSF
molecule including displaying the composition of

- 41 -

moieties of said G-CSF molecule, preferably displaying
the three dimensional location of each amino acid, and
more preferably displaying the three dimensional
location of each atom of a G-CSF molecule;

5   (b)   viewing said display;

            (c)   selecting a site on said display for
alteration in the composition of said molecule or the
location of a moiety; and

            (d)   preparing a G-CSF analog with such alteration.

10   The alteration may be selected based on the desired
structural characteristics of the end-product G-CSF
analog, and considerations for such design are described
in more detail below. Such considerations include the
location and compositions of hydrophobic amino acid

15   residues, particularly residues internal to the helical
structures of a G-CSF molecule which residues, when
altered, alter the overall structure of the internal
core of the molecule and may prevent receptor binding;
the location and compositions of external loop

20   structures, alteration of which may not affect the
overall structure of the G-CSF molecule.

            FIGURES 2-4 illustrate the overall three
dimensional conformation in different ways. The
topological diagram, the ribbon diagram, and the barrel

25   diagram all illustrate aspects of the conformation of
G-CSF.

            FIGURE 2 illustrates a comparison between
G-CSF and other molecules. There is a similarity of
architecture, although these growth factors differ in

30   the local conformations of their loops and bundle
geometrics. The up-up-down-down topology with two long
crossover connections is conserved, however, among all
six of these molecules, despite the dissimilarity in
amino acid sequence.

35

- 42 -

FIGURE 3 illustrates in more detail the
secondary structure of recombinant human G-CSF. This
ribbon diagram illustrates the handedness of the helices
and their positions relative to each other.

5   FIGURE 4 illustrates in a different way the
conformation of recombinant human G-CSF. This "barrel"
diagram illustrates the overall architecture of
recombinant human G-CSF.

        C.   Preparation of Analogs Using M13
10   Mutagenesis

        This example relates to the preparation of
G-CSF analogs using site directed mutagenesis techniques
involving the single stranded bacteriophage M13,
according to methods published in PCT Application No.
15   WO 85/00817 (Souza et al., published February 28, 1985,
herein incorporated by reference). This method
essentially involves using a single-stranded nucleic
acid template of the non-mutagenized sequence, and
binding to it a smaller oligonucleotide containing the
20   desired change in the sequence. Hybridization
conditions allow for non-identical sequences to
hybridize and the remaining sequence is filled in to be
identical to the original template. What results is a
double stranded molecule, with one of the two strands
25   containing the desired change. This mutagenized single
strand is separated, and used itself as a template for
its complementary strand. This creates a double
stranded molecule with the desired change.

        The original G-CSF nucleic acid sequence used
30   is presented in FIGURE 1, and the oligonucleotides
containing the mutagenized nucleic acid(s) are presented
in Table 2. Abbreviations used herein for amino acid
residues and nucleotides are conventional, see Stryer,
Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y.,
35   N.Y. 1988, inside back cover.

- 43 -

The original G-CSF nucleic acid sequence was
first placed into vector M13mp21. The DNA from single
stranded phage M13mp21 containing the original G-CSF
sequence was then isolated, and resuspended in water.
5   For each reaction, 200 ng of this DNA was mixed with a
1.5 pmole of phosphorylated oligonucleotide (Table 2)
and suspended in 0.1M Tris, 0.01M MgCl$_2$, 0.005M DTT,
0.1mM ATP, pH 8.0. The DNAs were annealed by heating to
65°C and slowly cooling to room temperature.
10   Once cooled, 0.5mM of each ATP, dATP, dCTP,
dGTP, TTP, 1 unit of T4 DNA ligase and 1 unit of Klenow
fragment of E. coli polymerase 1 were added to the 1
unit of annealed DNA in 0.1M Tris, 0.025M NaCl, 0.01M
MgCl$_2$, 0.01M DTT, pH 7.5.
15   The now double stranded, closed circular DNA
was used to transfect E. coli without further
purification. Plaques were screened by lifting the
plaques with nitrocellulose filters, and then
hybridizing the filters with single stranded DNA end-
20   labeled with P^{32} for 1 hour at 55-60°C. After
hybridization, the filters were washed at 0-3°C below
the melt temperature of the oligo (2°C for A-T, 4°C for
G-C) which selectively left autoradiography signals
corresponding to plaques with phage containing the
25   mutated sequence. Positive clones were confirmed by
sequencing.
           Set forth below are the oligonucleotides used
for each G-CSF analog prepared via the M13 mutagenesis
method. The nomenclature indicates the residue and the
30   position of the original amino acid (e.g., Lysine at
position 17), and the residue and position of the
substituted amino acid (e.g., arginine 17). A
substitution involving more than one residue is
indicated via superscript notation, with commas between
35   the noted positions or a semicolon indicating different
residues. Deletions with no substitutions are so noted.

- 44 -

The oligonucleotide sequences used for M13-based
mutagenesis are next indicated; these oligonucleotides
were manufactured synthetically, although the method of
preparation is not critical, any nucleic acid synthesis
5   method and/or equipment may be used. The length of the
oligo is also indicated. As indicated above, these
oligos were allowed to contact the single stranded phage
vector, and then single nucleotides were added to
complete the G-CSF analog nucleic acid sequence.

Table 2

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
Lys17->Arg17	CTT TCT GCT GCG TTG TCT GGA ACA	24	3
Lys24->Arg24	ACA GGT TCG TCG TAT CCA GGG TG	23	4
Lys35->Arg35	CAC TGC AAG AAC GTC TGT GCG CT	23	5
Lys41->Arg41	CGC TAC TTA CCG TCT GTG CCA TC	23	6
Lys17,24,35-> Arg17,24,35	CTT TCT GCT GCG TTG TCT GGA ACA	24	7
	ACA GGT TCG TCG TAT CCA GGG TG	23	8
	CAC TGC AAG AAC GTC TGT GCG CT	23	9
Lys17,24,41-> Arg17,24,41	CTT TCT GCT GCG TTG TCT GGA ACA	24	10
	ACA GGT TCG TCG TAT CCA GGG TG	23	11
	CGC TAC TTA CCG TCT GTC CCA TC	23	12
Lys17,35,41-> Arg17,35,41	CTT TCT GCT GCG TTG TCT GGA ACA	24	13
	CAC TGC AAG AAC GTC TGT GCG CT	23	14
	CGC TAC TTA CCG TCT GTG CCA TC	23	15
Lys24,35,41-> Arg24,35,41	ACA GGT TCG TCG TAT CCA GGG TG	23	16
	CAC TGC AAG AAC GTC TGT GCG CT	23	17
	CGC TAC TTA CCG TCT GTG CCA TC	23	18

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
Lys^{17,24,35,41}->	CTT TCT GCT GCG TTG TCT GGA ACA	24	19
Arg^{17,24,35,41}	ACA GGT TCG TCG TAT CCA GGG TG	23	20
	CAC TGC AAG AAC GTC TGT GCG CT	23	21
	CGC TAC TTA CCG TCT GTG CCA TC	23	22
Cys^{18}->Ala^{18}	TCT GCT GAA AGC TCT GGA ACA GG	23	23
Gln68->Glu68	CTT GTC CAT CTG AAG CTC TTC AG	23	24
Cys^{37,43}->	GAA AAA CTG TCC GCT ACT TAC AAA	37	25
Ser^{37,43}	CTG TCC CAT CCG G		
Gln26->Ala26	TTC GTA AAA TCG CGG GTG ACG G	22	26
Gln^{174}->Ala^{174}	TCA TCT GGC TGC GCC GTA ATA G	22	27
Arg^{170}->Ala^{170}	CCG TGT TCT GGC TCA TCT GGC T	22	28
Arg^{167}->Ala^{167}	GAA GTA TCT TAC GCT GTT CTG CGT	24	29
Deletion 167	GAA GTA TCT TAC TAA GTT CTG CGT C	25	30
Lys^{41}->Ala^{41}	CGC TAC TTA CGC ACT GTG CCA T	22	31
His^{44}->Lys^{44}	CAA ACT GTG CAA GCC GGA AGA G	22	32
Glu^{47}->Ala^{47}	CAT CCG GAA GCA CTG GTA CTG C	22	33

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length(nucleotide)	Seq. ID
Arg23->Ala23	GGA ACA GGT TGC TAA AAT CCA GG	23	34
Lys24->Ala24	GAA CAG GTT CGT GCG ATC CAG GGT G	25	35
Glu20->Ala20	GAA ATG TCT GGC ACA GGT TCG T	22	36
Asp28->Ala28	TCC AGG GTG CCG GTG CTG C	19	37
Met127->Glu127	AAG AGC TCG GTG AGG CAC CAG CT	23	38
Met138->Glu138	CTC AAG GTG CTG AGC CGG CAT TC	23	39
Met127->Leu127	GAG CTC GGT CTG GCA CCA GC	20	40
Met138->Leu138	TCA AGG TGC TCT GCC GGC ATT	21	41
Ser13->Ala13	TCT GCC GCA AGC CTT TCT GCT GA	23	42
Lys17->Ala17	CTT TCT GCT GGC ATG TCT GGA ACA	24	43
Gln121->Ala121	CTA TTT GGC AAG CGA TGG AAG AGC	24	44
Glu124->Ala124	CAG ATG GAA GCG CTC GGT ATG	21	45

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Met127,138->
Leu127,138	GAG CTC GGT CTG GCA CCA GC
TCA AGG TGC TCT GCC GGC ATT	20
21	46
47
**Glu20->Ala20;
Ser13->Gly13	GAA ATG TCT GGC ACA GGT TCG T	22	48

** This analog came about during the preparation of G-CSF analog Glu20->Ala20. As several clones were being sequenced to identify the Glu20->Ala20 analog, the Glu20->Ala20; Ser13->Gly13 analog was identified. This double mutant was the result of an in vitro Klenow DNA polymerase reaction mistake.

- 49 -

D.   Preparation of G-CSF Analogs Using
DNA Amplification

      This example relates to methods for producing
G-CSF analogs using a DNA amplification technique.
5 Essentially, DNA encoding each analog was amplified in
two separate pieces, combined, and then the total
sequence itself amplified. Depending upon where the
desired change in the original G-CSF DNA was to be made,
internal primers were used to incorporate the change,
10 and generate the two separate amplified pieces. For
example, for amplification of the 5' end of the desired
analog DNA, a 5' flanking primer (complementary to a
sequence of the plasmid upstream from the G-CSF original
DNA) was used at one end of the region to be amplified,
15 and an internal primer, capable of hybridizing to the
original DNA but incorporating the desired change, was
used for priming the other end. The resulting amplified
region stretched from the 5' flanking primer through the
internal primer. The same was done for the 3' terminus,
20 using a 3' flanking primer (complementary to a sequence
of the plasmid downstream from the G-CSF original DNA)
and an internal primer complementary to the region of
the intended mutation. Once the two "halves" (which may
or may not be equal in size, depending on the location
25 of the internal primer) were amplified, the two "halves"
were allowed to connect. Once connected, the 5'
flanking primer and the 3' flanking primer were used to
amplify the entire sequence containing the desired
change.
30   If more than one change is desired, the above
process may be modified to incorporate the change into
the internal primer, or the process may be repeated
using a different internal primer. Alternatively, the
gene amplification process may be used with other
35 methods for creating changes in nucleic acid sequence,
such as the phage based mutagenesis technique as

- 50 -

described above. Examples of process for preparing
analogs with more than one change are described below.

To create the G-CSF analogs described below,
the template DNA used was the sequence as in FIGURE 1
5   plus certain flanking regions (from a plasmid containing
the G-CSF coding region). These flanking regions were
used as the 5' and 3' flanking primers and are set forth
below.   The amplification reactions were performed in
40 ul volumes containing 10 mM Tris-HCl, 1.5 mM MgCl$_2$,
10   50 mM KCl, 0.1 mg/ml gelatin, pH 8.3 at 20°C. The 40 ul
reactions also contained 0.1mM of each dNTP, 10 pmoles
of each primer, and 1 ng of template DNA. Each
amplification was repeated for 15 cycles. Each cycle
consisted of 0.5 minutes at 94°C, 0.5 minutes at 50°C,
15   and 0.75 minutes at 72°C. Flanking primers were 20
nucleotides in length and internal primers were 20 to 25
nucleotides in length. This resulted in multiple copies
of double stranded DNA encoding either the front portion
or the back portion of the desired G-CSF analog.
20   For combining the two "halves," one fortieth
of each of the two reactions was combined in a third DNA
amplification reaction. The two portions were allowed
to anneal at the internal primer location, as their ends
bearing the mutation were complementary, and following a
25   cycle of polymerization, give rise to a full length DNA
sequence. Once so annealed, the whole analog was
amplified using the 5' and 3' flanking primers. This
amplification process was repeated for 15 cycles as
described above.
30   The completed, amplified analog DNA sequence
was cleaved with XbaI and XhoI restriction endonuclease
to produce cohesive ends for insertion into a vector.
The cleaved DNA was placed into a plasmid vector, and
that vector was used to transform E. coli.
35   Transformants were challenged with kanamycin at 50 ug/ml
and incubated at 30°C. Production of G-CSF analog

- 51 -

protein was confirmed by polyacrylamide gel
electrophoresis of a whole cell lysate. The presence of
the desired mutation was confirmed by DNA sequence
analysis of plasmid purified from the production
5   isolate. Cultures were then grown, and cells were
harvested, and the G-CSF analogs were purified as set
forth below.

        Set forth below in Table 3 are the specific
primers used for eachanalog made using gene
10 amplification.

Table 3

	Analog Seq. ID	Internal Primer(5'->3')	
15	His^{44}->Ala^{44}	5'primer-TTCCGGAGCGCACAGTTTG	49
		3'primer-CAAACTGTGGGCTCCGGAAGAGC	50
	Thr^{117}->Ala^{117}	5'primer-ATGCCAAATTGCAGTAGCAAAG	51
		3'primer-CTTTGCTACTGCAATTTGGCAACA	52
20	Asp^{110}->Ala^{110}	5'primer-ATCAGCTACTGCTAGCTGCAGA	53
		3'primer-TCTGCAGCTAGCAGTAGCTGACT	54
	Gln^{21}->Ala^{21}	5'primer-TTACGAACCGCTTCCAGACATT	55
25		3'primer-AATGTCTGGAAGCGGTTCGTAAAAT	56
	Asp^{113}->Ala^{113}	5'primer-GTAGCAAATGCAGCTACATCTA	57
		3'primer-TAGATGTAGCTGCATTTGCTACTAC	58
30	His^{53}->Ala^{53}	5'primer-CCAAGAGAAGCACCCAGCAG.	59
		3'primer-CTGCTGGGTGCTTCTCTTGGGA	60

        For each analog, the following 5' flanking
        primer was used:
        5'-CACTGGCGGTGATAATGAGC   61

- 52 -

(Table 3 con't)

     For each analog, the following 3' flanking
     primer was used:
5   3'-GGTCATTACGGACCGGATC   62

               1.   Construction of Double Mutation
                 To make G-CSF analog Gln^{12,21}->Glu^{12,21}, two
     separate DNA amplifications were conducted to create the
10   two DNA mutations. The template DNA used was the
     sequence as in FIGURE 1 plus certain flanking regions
     (from a plasmid containing the G-CSF coding region).
     The precise sequences are listed below. Each of the two
     DNA amplification reactions were carried out using a
15   Perkin Elmer/Cetus DNA Thermal Cycler. The 40 ul
     reaction mix consisted of 1X PCR Buffer (Cetus), 0.2 mM
     each of the 4 dXTPs (Cetus), 50 pmoles of each primer
     oligonucleotide, 2 ng of G-CSF template DNA (on a
     plasmid vector), and 1 unit of Taq polymerase (Cetus).
20   The amplification process was carried out for 30 cycles.
     Each cycle consisted of 1minute at 94°C, 2 minutes at
     50°C, and 3 minutes at 72°C.
                 DNA amplification "A" used the oligonucleotides:
     5' CCACTGGCGGTGATACTGAGC 3' (Seq. ID 63) and
25   5' AGCAGAAAGCTTTCCGGCAGAGAAGAAGCAGGA 3' (Seq. ID 64)
                 DNA amplification "B" used the oligonucleotides:
     5' GCCGCAAAGCTTTCTGCTGAAATGTCTGGAAGAGGTTCGTAAAATCCAGGGTGA 3'
     (Seq. ID 65) and
     5' CTGGAATGCAGAAGCAAATGCCGGCATAGCACCTTCAGTCGGTTGCAGAGCTGGTGCCA 3'
30   (Seq. ID 66)
                 From the 109 base pair double stranded DNA
     product obtained after DNA amplification "A", a 64 base
     pair XbaI to HindIII DNA fragment was cut and isolated
     that contained the DNA mutation Gln^{12}->Glu^{12}. From the
35   509 base pair double stranded DNA product obtained after
     DNA amplification "B", a 197 base pair HindIII to BsmI

- 53 -

DNA fragment was cut and isolated that contained the DNA
mutation Gln^{21}->Glu^{21}.

The "A" and "B" fragments were ligated
together with a 4.8 kilo-base pair XbaI to BsmI DNA
5   plasmid vector fragment. The ligation mix consisted of
equal molar DNA restriction fragments, ligation buffer
(25 mM Tris-HCl pH 7.8, 10 mM MgCl$_2$, 2 mM DTT, 0.5 mM
rATP, and 100 ug/ml BSA) and T4 DNA ligase and was
incubated overnight at 14°C. The ligated DNA was then
10 transformed into E. coli FM5 cells by electroporation
using a Bio Rad Gene Pulsar apparatus (BioRad, Richmond,
CA). A clone was isolated and the plasmid construct
verified to contain the two mutations by DNA sequencing.
This 'intermediate' vector also contained a deletion of
15 a 193 base pair BsmI to BsmI DNA fragment. The final
plasmid vector was constructed by ligation and
transformation (as described above) of DNA fragments
obtained by cutting and isolating a 2 kilo-base pair
SstI to BamHI DNA fragment from the intermediate vector,
20 a 2.8 kbp SstI to EcoRI DNA fragment from the plasmid
vector, and a 360 bp BamHI to EcoRI DNA fragment from
the plasmid vector. The final construct was verified by
DNA sequencing the G-CSF gene. Cultures were grown, and
the cells were harvested, and the G-CSF analogs were
25 purified as set forth below.

As indicated above, any combination of
mutagenesis techniques may be used to generate a G-CSF
analog nucleic acid (and expression product) having one
or more than one alteration. The two examples above,
30 using M13-based mutagenesis and gene amplification-based
mutagenesis, are illustrative.

E.   Expression of G-CSF Analog DNA

The G-CSF analog DNAs were then placed into a
plasmid vector and used to transform E. coli strain FM5
35 (ATCC#53911). The present G-CSF analog DNAs contained
on plasmids and in bacterial host cells are available

- 54 -

from the American Type Culture Collection, Rockville,
MD, and the accession designations are indicated below.

One liter cultures were grown in broth
containing 10g tryptone, 5g yeast extract and 5g NaCl)
5   at 30°C until reaching a density at A^{600} of 0.5, at which
point they were rapidly heated to 42°C. The flasks were
allowed to continue shaking at for three hours.

Other prokaryotic or eukaryotic host cells may
also be used, such as other bacterial cells, strains or
10   species, mammalian cells in culture (COS, CHO or other
types) insect cells or multicellular organs or
organisms, or plant cells or multicellular organs or
organisms, and a skilled practitioner will recognize the
appropriate host. The present G-CSF analogs and related
15   compositions may also be prepared synthetically, as, for
example, by solid phase peptide synthesis methds, or
other chemical manufacturing techniques. Other cloning
and expression systems will be apparent to those skilled
in the art.

20   F.   <u>Purification of G-CSF Analog Protein</u>

Cells were harvested by centrifugation (10,000
x G, 20 minutes, 4°C). The pellet (usually 5 grams) was
resuspended in 30 ml of 1mM DTT and passed three times
through a French press cell at 10,000 psi. The broken
25   cell suspension was centrifuged at 10,000g for 30
minutes, the supernatant removed, and the pellet
resuspended in 30-40 ml water. This was recentrifuged
at 10,000 x G for 30 minutes, and this pellet was
dissolved in 25 ml of 2% Sarkosyl and 50mM Tris at pH 8.
30   Copper sulfate was added to a concentration of 40uM, and
the mixture was allowed to stir for at least 15 hours at
15-25°C. The mixture was then centrifuged at 20,000 x G
for 30 minutes. The resultant solubilized protein
mixture was diluted four-fold with 13.3 mM Tris, pH 7.7,
35   the Sarkosyl was removed, and the supernatant was then
applied to a DEAE-cellulose (Whatman DE-52) column

- 55 -

equilibrated in 20mM Tris, pH 7.7. After loading and
washing the column with the same buffer, the analogs
were eluted with 20mM Tris /NaCl (between 35mM to 100mM
depending on the analog, as indicated below), pH 7.7.

5   For most of the analogs, the eluent from the DEAE column
was adjusted to a pH of 5.4, with 50% acetic acid and
diluted as necessary (to obtain the proper conductivity)
with 5mM sodium acetate pH 5.4. The solution was then
loaded onto a CM-sepharose column equilibrated in 20 mM

10   sodium acetate, pH 5.4. The column was then washed with
20mM NaAc, pH 5.4 until the absorbance at 280 nm was
approximately zero. The G-CSF analog was then eluted
with sodium acetate/NaCl in concentrations as described
below in Table 4. The DEAE column eluents for those

15   analogs not applied to the CM-sepharose column were
dialyzed directly into 10mM NaAc, ph 4.0 buffer. The
purified G-CSF analogs were then suitably isolated for
in vitro analysis. The salt concentrations used for
eluting the analogs varied, as noted above. Below, the

20   salt concentrations for the DEAE cellulose column and
for the CM-sepharose column are listed:

<u>Table 4</u>

25   <u>Salt Concentrations</u>

<u>Analog</u>	<u>DEAE Cellulose</u>	<u>CM-Sepharose</u>
$Lys^{17}->Arg^{17}$	35mM	37.5mM
$Lys^{24}->Arg^{24}$	35mM	37.5mM
$Lys^{35}->Arg^{35}$	35mM	37.5mM
$Lys^{41}->Arg^{41}$	35mM	37.5mM
$Lys^{17,24,35}->Arg^{17,24,35}$	35mM	37.5mM
$Lys^{17,35,41}->Arg^{17,35,41}$	35mM	37.5mM

- 56 -

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
Lys^{24,35,41}->Arg^{24,35,41}	35mM	37.5mM
Lys^{17,24,35,41}->Arg^{17,24,35,41}	35mM	37.5mM
Lys^{17,24,41}->Arg^{17,24,41}	35mM	37.5mM
Gln^{68}->Glu^{68}	60mM	37,5mM
Cys^{37,43}->Ser^{37,43}	40mM	37.5mM
Gln^{26}->Ala^{26}	40mM	40mM
Gln^{174}->Ala^{174}	40mM	40mM
Arg^{170}->Ala^{170}	40mM	40mM
Arg^{167}->Ala^{167}	40mM	40mM
Deletion 167*	N/A	N/A
Lys^{41}->Ala^{41}	160mM	40mM
His^{44}->Lys^{44}	40mM	60mM
Glu^{47}->Ala^{47}	40mM	40mM
Arg^{23}->Ala^{23}	40mM	40mM
Lys^{24}->Ala^{24}	120mM	40mM
Glu^{20}->Ala^{20}	40mM	60mM
Asp^{28}->Ala^{28}	40mM	80mM
Met^{127}->Glu^{127}	80mM	40mM
Met^{138}->Glu^{138}	80mM	40mM
Met^{127}->Leu^{127}	40mM	40mM
Met^{138}->Leu^{138}	40mM	40mM
Cys^{18}->Ala^{18}	40mM	37.5mM
Gln^{12,21}->Glu^{12,21}	60mM	37.5mM
Gln^{12,21,68}->Glu^{12,21,68}	60mM	37.5mM
Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	40mM	80mM

- 57 -

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Met^{127,138}->Leu^{127,138}$	40mM	40mM
$Ser^{13}->Ala^{13}$	40mM	40mM
$Lys^{17}->Ala^{17}$	80mM	40mM
$Gln^{121}->Ala^{121}$	40mM	60mM
$Gln^{21}->Ala^{21}$	50mM	Gradient 0 -150mM
$His^{44}->Ala^{44}**$	40mM	N/A
$His^{53}->Ala^{53}**$	50mM	N/A
$Asp^{110}->Ala^{110}**$	40mM	N/A
$Asp^{113}->Ala^{113}**$	40mM	N/A
$Thr^{117}->Ala^{117}**$	50mM	N/A
$Asp^{28}->Ala^{28};$ Asp^{110} $Ala^{110}**$	50mM	N/A
$Glu^{124}->Ala^{124}**$	40mM	40mM

* For Deletion ^{167}, the data are unavailable.
** For these analogs, the DEAE cellulose column alone
was use for purification.

5   The above purification methods are
illustrative, and a skilled practitioner will recognize
that other means are available for obtaining the present
G-CSF analogs.

          G.   Biological Assays
10   Regardless of which methods were used to
create the present G-CSF analogs, the analogs were
subject to assays for biological activity. Tritiated
thymidine assays were conducted to ascertain the degree
of cell division. Other biological assays, however, may
15   be used to ascertain the desired activity. Biological
assays such as assaying for the ability to induce
terminal differentiation in mouse WEHI-3B (D+) leukemic
cell line, also provides indication of G-CSF activity.

- 58 -

See Nicola, et al., Blood 54: 614-27 (1979). Other in
vitro assays may be used to ascertain biological
activity. See Nicola, Annu. Rev. Biochem. 58: 45-77
(1989). In general, the test for biological activity

5   should provide analysis for the desired result, such as
increase or decrease in biological activity (as compared
to non-altered G-CSF), different biological activity (as
compared to non-altered G-CSF), receptor affinity
analysis, or serum half-life analysis. The list is

10   incomplete, and those skilled in the art will recognize
other assays useful for testing for the desired end
result.

The ^{3}H-thymidine assay was performed using
standard methods. Bone marrow was obtained from

15   sacrificed female Balb C mice. Bone marrow cells were
briefly suspended, centrifuged, and resuspended in a
growth medium. A 160 ul aliquot containing
approximately 10,000 cells was placed into each well of
a 96 well micro-titer plate. Samples of the purified

20   G-CSF analog(as prepared above) were added to each well,
and incubated for 68 hours. Tritiated thymidine was
added to the wells and allowed to incubate for 5
additional hours. After the 5 hour incubation time, the
cells were harvested, filtered, and thoroughly rinsed.

25   The filters were added to a vial containing
scintillation fluid. The beta emissions were counted
(LKB Betaplate scintillation counter). Standards and
analogs were analyzed in triplicate, and samples which
fell substantially above or below the standard curve

30   were re-assayed with the proper dilution. The results
reported here are the average of the triplicate analog
data relative to the unaltered recombinant human G-CSF
standard results.

H.   HPLC Analysis

35   High pressure liquid chromatography was
performed on purified samples of analog. Although peak

- 59 -

position on a reverse phase HPLC column is not a
definitive indication of structural similarity between
two proteins, analogs which have similar retention times
may have the same type of hydrophobic interactions with
5   the HPLC column as the non-altered molecule. This is
one indication of an overall similar structure.

Samples of the analog and the non-altered
recombinant human G-CSF were analyzed on a reverse phase
(0.46 x 25 cm) Vydac 214TP54 column (Separations Group,
10   Inc. Hesperia, CA). The purified analog G-CSF samples
were prepared in 20 mM acetate and 40 mM NaCl solution
buffered at pH 5.2 to a final concentration of 0.1 mg/ml
to 5 mg/ml, depending on how the analog performed in the
column. Varying amounts (depending on the
15   concentration) were loaded onto the HPLC column, which
had been equilibrated with an aqueous solution
containing 1% isopropanol, 52.8% acetonitrile, and .38%
trifluoro acetate (TFA). The samples were subjected to
a gradient of 0.86%/minute acetonitrile, and .002% TFA.
20   I. Results

Presented below are the results of the above
biological assays and HPLC analysis. Biological
activity is the average of triplicate data and reported
as a percentage of the control standard (non-altered
25   G-CSF). Relative HPLC peak position is the position of
the analog G-CSF relative to the control standard (non-
altered G-CSF) peak. The "+" or "-" symbols indicate
whether the analog HPLC peak was in advance of or
followed the control standard peak (in minutes). Not
30   all of the variants had been analyzed for relative HPLC
peak, and only those so analyzed are included below.
Also presented are the American Type Culture Collection
designations for E. coli host cells containing the
nucleic acids coding for the present analogs, as
35   prepared above.

Table 5

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
67	1	Lys^{17}->Arg^{17}	N/A	69184	N/A
68	2	Lys^{24}->Arg^{24}	N/A	69185	N/A
69	3	Lys^{35}->Arg^{35}	N/A	69186	N/A
70	4	Lys^{41}->Arg^{41}	N/A	69187	N/A
71	5	Lys^{17,24,35}->Arg^{17,24,35}	N/A	69189	N/A
72	6	Lys^{17,35,41}->Arg^{17,35,41}	N/A	69192	N/A
73	7	Lys^{24,35,41}->Arg^{24,35,41}	N/A	69191	N/A
74	8	Lys^{17,24,35,41} ->Arg^{17,24,35,41}	N/A	69193	N/A
75	9	Lys^{17,24,41}->Arg^{17,24,41}	N/A	69190	N/A
76	10	Gln^{68}->Glu^{68}	N/A	69196	N/A
77	11	Cys^{37,43}->Ser^{37,43}	N/A	69197	N/A
78	12	Gln^{26}->Ala^{26}	+.96	69201	51%
79	13	Gln^{174}->Ala^{174}	+.14	69202	100%
80	14	Arg^{170}->Ala^{170}	+.78	69203	100%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
81	15	Arg^{167}->Ala^{167}	+.54	69204	110%
82	16	Deletion 167	-.99	69207	N/A
83	17	Lys^{41}->Ala^{41}	+.25	69208	81%
84	18	His^{44}->Lys^{44}	-1.53	69212	70%
85	19	Glu^{47}->Ala^{47}	+.14	69205	0%
86	20	Arg^{23}->Ala^{23}	-.03	69206	31%
87	21	Lys^{24}->Ala^{24}	+1.95	69213	0%
88	22	Glu^{20}->Ala^{20}	-0.07	69211	0%
89	23	Asp^{28}->Ala^{28}	-.30	69210	147%
90	24	Met^{127}->Glu^{127}	N/A	69223	N/A
91	25	Met^{138}->Glu^{138}	N/A	69222	N/A
92	26	Met^{127}->Leu^{127}	N/A	69198	N/A
93	27	Met^{138}->Leu^{138}	N/A	69199	N/A
94	28	Cys^{18}->Ala^{18}	N/A	69188	N/A
95	29	Gln^{12,21}->Glu^{12,21}	N/A	69194	N/A
96	30	Gln^{12,21,68}->Glu^{12,21,68}	N/A	69195	N/A
97	31	Glu^{20}->Ala^{20}; Ser^{13}	+1.74	69209	0%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
		->Gly13			
98	32	Met127,138->Leu127,138	+1.43	69200	98%
99	33	Ser13->Ala13	0	69221	110%
100	34	Lys17->Ala17	+.50	69226	70%
101	35	Gln121->Ala121	+2.7	69225	100%
102	36	Gln21->Ala21	+0.63	69217	9.6%
103	37	His44->Ala44	+1.52	69215	10.8%
104	38	His53->Ala53	+0.99	69219	8.3%
105	39	Asp110->Ala110	+1.97	69216	29%
106	40	Asp113->Ala113	-0.34	69218	0%
107	41	Thr117->Ala117	+0.4	69214	9.7%
108	42	Asp28->Ala28; Asp110 Ala110	+3.2	69220	20.6%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
109	43	Glu124->Ala124	+0.16	69224	75%
110	44	Phe114->Val 114, T117->A117**	+0.53		0%

**This analog was apparently a result of an inadvertent error in the oligo which was used to prepare number 41, above (Thr117->Ala 117), and thus was prepared identically to the process used for that analog.

"N/A" indicates data which are not available.

- 64 -

1. Identification of Structure-Function
Relationships

        The first step used to design the present
analogs was to determine what moieties are necessary for
5   structural integrity of the G-CSF molecule. This was
done at the amino acid residue level, although the
atomic level is also available for analysis.
Modification of the residues necessary for structural
integrity results in change in the overall structure of
10   the G-CSF molecule. This may or may not be desirable,
depending on the analog one wishes to produce. The
working examples here were designed to maintain the
overall structural integrity of the G-CSF molecule, for
the purpose of maintain G-CSF receptor binding of the
15   analog to the G-CSF receptor (as used in this section
below, the "G-CSF receptor" refers to the natural G-CSF
receptor, found on hematopoietic cells). It was
assumed, and confirmed by the studies presented here,
that G-CSF receptor binding is a necessary step for at
20   least one biological activity, as determined by the
above biological assays.

        As can be seen from the figures, G-CSF (here,
recombinant human met-G-CSF) is an antiparallel 4-alpha
helical bundle with a left-handed twist, and with
25   overall dimensions of 45 Å x 30Å x 24Å. The four
helices within the bundle are referred to as helices A,
B, C and D, and their connecting loops are known as the
AB, BC and CD loops. The helix crossing angles range
from -167.5° to -159.4°. Helices A, B, and C are
30   straight, whereas helix D contains two kinds of
structural characteristics, at Gly 150 and Ser 160 (of
the recombinant human met-G-CSF). Overall, the G-CSF
molecules is a bundle of four helices, connected in
series by external loops. This structural information
35   was then correlated with known functional information.
It was known that residues (including methionine at

- 65 -

position 1) 47, 23, 24, 20, 21, 44, 53, 113, 110, 28 and
114 may be modified, and the effect on biological
activity would be substantial.

     The majority of single mutations which lowered
5 biological activity were centered around two regions of
G-CSF that are separated by 30Å, and are located on
different faces of the four helix bundle. One region
involves interactions between the A helix and the D
helix. This is further confirmed by the presence of
10 salt bridges in the non-altered molecule as follows:

Atom	Helix	Atom	Helix	Distance
Arg 170 N1	D	Tyr 166 OH	A	3.3
Tyr 166 OH	D	Arg 23 N2	A	3.3
Glu 163 OE1	D	Arg 23 N1	A	2.8
Arg 23 N1	A	Gln 26 OE1	A	3.1
Gln 159 NE2	D	Gln 26 O	A	3.3

     Distances reported here were for molecule A,
as indicated in FIGURE 5 (wherein three G-CSF molecules
15 crystallized together and were designated as A, B, and
C). As can be seen, there is a web of salt bridges
between helix A and helix D, which act to stabilize the
helix A structure, and therefore affect the overall
structure of the G-CSF molecule.
20   The area centering around residues Glu 20, Arg
23 and Lys 24 are found on the hydrophilic face of the A
helix (residues 20-37). Substitution of the residues
with the non-charged alanine residue at positions 20 and
23 resulted in similar HPLC retention times, indicating
25 similarity in structure. Alteration of these sites
altered the biological activity (as indicated by the
present assays). Substitution at Lys 24 altered
biological activity, but did not result in a similar
HPLC retention time as the other two alterations.

- 66 -

The second site at which alteration lowered biological activity involves the AB helix. Changing glutamine at position 47 to alanine (analog no. 19, above) reduced biological activity (in the thymidine

5 uptake assay) to zero. The AB helix is predominantly hydrophobic, except at the amino and carboxy termini; it contains one turn of a 3^{10} helix. There are two histadines at each termini (His 44 and His 56) and an additional glutamate at residue 46 which has the

10 potential to form a salt bridge to His 44. The fourier transformed infra red spectrographic analysis (FTIR) of the analog suggests this analog is structurally similar to the non-altered recombinant G-CSF molecule. Further testing showed that this analog would not crystallize

15 under the same conditions as the non-altered recombinant molecule.

Alterations at the carboxy terminus (Gln 174, Arg 167 and Arg 170) had little effect on biological activity. In contrast, deletion of the last eight

20 residues (167-175) lowered biological activity. These results may indicate that the deletion destabilizes the overall structure which prevents the mutant from proper binding to the G-CSF receptor (and thus initiating signal transduction).

25 Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops -- the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being

30 position 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops -- the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the

35 internal hydrophobic residues are (with methionine being position 1 as in FIGURE 1) Phe 14, Cys 18, Val 22, Ile

- 67 -

25, Ile 32 and Leu 36. The other hydrophobic residues
(again with the met at position 1) are: helix B, Ala
72, Leu 76, Leu 79, Leu 83, Tyr 86, Leu 90 Leu 93; helix
C, Leu 104, Leu 107, Val 111, Ala 114, Ile 118, Met 122;
5   and helix D, Val 154, Val 158, Phe 161, Val 164, Val
168, Leu 172.

            The above biological activity data, from the
presently prepared G-CSF analogs, demonstrate that
modification of the external loops interfere least with
10 G-CSF overall structure. Preferred loops for analog
prepration are the AB loop and the CD loop. The loops
are relatively flexible structures as compared to the
helices. The loops may contribute to the proteolysis of
the molecule. G-CSF is relatively fast acting in vivo
15 as the purpose the molecule serves is to generate a
response to a biological challenge, i.e., selectively
stimulate neutrophils. The G-CSF turnover rate is also
relatively fast. The flexibility of the loops may
provide a "handle" for proteases to attach to the
20 molecule to inactivate the molecule. Modification of
the loops to prevent protease degradation, yet have (via
retention of the overall structure of non-modified
G-CSF) no loss in biological activity may be
accomplished.
25   This phenomenon is probably not limited to the
G-CSF molecule but may also be common to the other
molecules with known similar overall structures, as
presented in Figure 2. Alteration of the external loop
of, for example hGH, Interferon B, IL-2, GM-CSF and IL-4
30 may provide the least change to the overall structure.
The external loops on the GM-CSF molecule are not as
flexible as those found on the G-CSF molecule, and this
may indicate a longer serum life, consistent with the
broader biological activity of GM-CSF. Thus, the
35 external loops of GM-CSF may be modified by releasing
the external loops from the beta-sheet structure, which

- 68 -

may make the loops more flexible (similar to those
G-CSF) and therefore make the molecule more susceptible
to protease degradation (and thus increase the turnover
rate).

5   Alteration of these external loops may be
effected by stabilizing the loops by connection to one
or more of the internal helices. Connecting means are
known to those in the art, such as the formation of a
beta sheet, salt bridge, disulfide bonding or
10   hydrophobic interactions, and other means are available.
Also, deletion of one or more moieties, such as one or
more amino acid residues or portions thereof, to prepare
an abbreviated molecule and thus eliminate certain
portions of the external loops may be effected.
15   Thus, by alteration of the external loops,
preferably the AB loop (amino acids 58-72 of r-hu-met
G-CSF) or the CD loop (amino acids 119 to 145 of
r-hu-met-G-CSF), and less preferably the amino terminus
(amino acids 1-10), one may therefore modify the
20   biological function without elimination of G-CSF G-CSF
receptor binding. For example, one may: (1) increase
half-life (or prepare an oral dosage form, for example)
of the G-CSF molecule by, for example, decreasing the
ability of proteases to act on the G-CSF molecule or
25   adding chemical modifications to the G-CSF molecule,
such as one or more polyethylene glycol molecules or
enteric coatings for oral formulation which would act to
change some characteristic of the G-CSF molecule as
described above, such as increasing serum or other half-
30   life or decreasing antigenicity; (2) prepare a hybrid
molecule, such as combining G-CSF with part or all of
another protein such as another cytokine or another
protein which effects signal transduction via entry
through the cell through a G-CSF G-CSF receptor
35   transport mechanism; or (3) increase the biological
activity as in, for example, the ability to selectively

- 69 -

stimulate neutrophils (as compared to a non-modified
G-CSF molecule). This list is not limited to the above
exemplars.

Another aspect observed from the above data is
5   that stabilizing surface interactions may affect
biological activity. This is apparent from comparing
analogs 23 and 40. Analog 23 contains a substitution of
the charged asparagine residue at position 28 for the
neutrally-charged alanine residue in that position, and
10 such substitution resulted in a 50% increase in the
biological activity (as measured by the disclosed
thymidine uptake assays). The asparagine residue at
position 28 has a surface interaction with the
asparagine residue at position 113; both residues being
15 negatively charged, there is a certain amount of
instability (due to the repelling of like charged
moieties). When, however the asparagine at position 113
is replaced with the neutrally-charged alanine, the
biological activity drops to zero (in the present assay
20 system). This indicates that the asparagine at position
113 is critical to biological activity, and elimination
of the asparagine at position 28 serves to increase the
effect that asparagine at position 113 possesses.

The domains required for G-CSF receptor
25 binding were also determined based on the above analogs
prepared and the G-CSF structure. The G-CSF receptor
binding domain is located at residues (with methionine
being position 1) 11-57 (between the A and AB helix) and
100-118 (between the B and C helices). One may also
30 prepare abbreviated molecules capable of binding to a
G-CSF receptor and initiate signal transduction for
selectively stimulating neutrophils by changing the
external loop structure and having the receptor binding
domains remain intact.

35   Residues essential for biological activity and
presumably G-CSF receptor binding or signal transduction

- 70 -

have been identified. Two distinct sites are located on
two different regions of the secondary structure. What
is here called "Site A" is located on a helix which is
constrained by salt bridge contacts between two other
5   members of the helical bundle. The second site, "Site B"
is located on a relatively more flexible helix, AB. The
AB helix is potentially more sensitive to local pH
changes because of the type and position of the residues
at the carboxy and amino termini. The functional
10   importance of this flexible helix may be important in a
conformationally induced fit when binding to the G-CSF
receptor. Additionally, the extended portion of the D
helix is also indicated to be a G-CSF receptor binding
domain, as ascertained by direct mutational and indirect
15   comparative protein structure analysis. Deletion of the
carboxy terminal end of r-hu-met-G-CSF reduces activity
as it does for hGH, see, Cunningham and Wells, Science
244: 1081-1084 (1989). Cytokines which have similar
structures, such as IL-6 and GM-CSF with predicted
20   similar topology also center their biological activity
along the carboxy end of the D helix, see Bazan,
Immunology Today 11: 350-354 (1990)

A comparison of the structures and the
positions of G-CSF receptor binding determinants between
25   G-CSF and hGH suggests both molecules have similar means
of signal transduction. Two separate G-CSF receptor
binding sites have been identified for hGH De Vos et
al., Science 255: 306-32 (1991). One of these binding
sites (called "Site I") is formed by residues on the
30   exposed faces of hGH's helix 1, the connection region
between helix 1 and 2, and helix 4. The second binding
site (called "Site II") is formed by surface residues of
helix 1 and helix 3.

The G-CSF receptor binding determinates
35   identified for G-CSF are located in the same relative
positions as those identified for hGH. The G-CSF

receptor binding site located in the connecting region
between helix A and B on the AB helix (Site A) is
similar in position to that reported for a small piece
of helix (residues 38-47) of hGH. A single point
5   mutation in the AB helix of G-CSF significantly reduces
biological activity (as ascertained in the present
assays), indicating the role in a G-CSF receptor-ligand
interface. Binding of the G-CSF receptor may
destabilize the 3^{10} helical nature of this region and
10   induce a conformation change improving the binding
energy of the ligand/G-CSF receptor complex.

In the hGH receptor complex, the first helix
of the bundle donates residues to both of the binding
sites required to dimerize the hGH receptor Mutational
15   analysis of the corresponding helix of G-CSF (helix A)
has identified three residues which are required for
biological activity. Of these three residues, Glu 20
and Arg 24 lie on one face of the helical bundle towards
helix C, whereas the side chain of Arg 23 (in two of the
20   three molecules in the asymmetric unit) points to the
face of the bundle towards helix D. The position of
side chains of these biologically important residues
indicates that similar to hGH, G-CSF may have a second
G-CSF receptor binding site along the interface between
25   helix A and helix C. In contrast with the hGH molecule,
the amino terminus of G-CSF has a limited biological
role as deletion of the first 11 residues has little
effect on the biological activity.

As indicated above (see FIGURE 2, for
30   example), G-CSF has a topological similarity with other
cytokines. A correlation of the structure with previous
biochemical studies, mutational analysis and direct
comparison of specific residues of the hGH receptor
complex indicates that G-CSF has two receptor binding
35   sites. Site A lies along the interface of the A and D
helices and includes residues in the small AB helix.

- 72 -

Site B also includes residues in the A helix but lies along the interface between helices A and C. The conservation of structure and relative positions of biologically important residues between G-CSF and hGH is

5   one indication of a common method of signal transduction in that the receptor is bound in two places. It is therefore found that G-CSF analogs possessing altered G-CSF receptor binding domains may be prepared by alteration at either of the G-CSF receptor binding sites

10   (residues 20-57 and 145-175).

Knowledge of the three dimensional structure and correlation of the composition of G-CSF protein makes possible a systematic, rational method for preparing G-CSF analogs. The above working examples

15   have demonstrated that the limitations of the size and polarity of the side chains within the core of the structure dictate how much change the molecule can tolerate before the overall structure is changed.

- 73 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

    (i) APPLICANT: Amgen Inc.

    (ii) TITLE OF INVENTION: G-CSF ANALOG COMPOSITIONS AND METHODS

    (iii) NUMBER OF SEQUENCES: 110

    (iv) CORRESPONDENCE ADDRESS:
        (A) ADDRESSEE: Amgen, Inc.
        (B) STREET: Amgen Center, 1840 DeHavilland Drive
        (C) CITY: Thousand Oaks
        (D) STATE: California
        (E) COUNTRY: United States of America
        (F) ZIP: 91320-1789

    (v) COMPUTER READABLE FORM:
        (A) MEDIUM TYPE: Floppy disk
        (B) COMPUTER: IBM PC compatible
        (C) OPERATING SYSTEM: PC-DOS/MS-DOS
        (D) SOFTWARE: PatentIn Release #1.0, Version #1.25

    (vi) CURRENT APPLICATION DATA:
        (A) APPLICATION NUMBER:
        (B) FILING DATE:
        (C) CLASSIFICATION:

    (viii) ATTORNEY/AGENT INFORMATION:
        (A) NAME: Pessin, Karol
        (B) REGISTRATION NUMBER: 34,899

    (ix) TELECOMMUNICATION INFORMATION:
        (A) TELEPHONE: 805/499-5725
        (B) TELEFAX: 805/499-8011

(2) INFORMATION FOR SEQ ID NO:1:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 565 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA (genomic)

    (ix) FEATURE:
        (A) NAME/KEY: CDS
        (B) LOCATION: 30..554

- 74 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
TCTAGAAAAA ACCAAGGAGG TAATAAATA ATG ACT CCA TTA GGT CCT GCT TCT        53
                                    Met Thr Pro Leu Gly Pro Ala Ser
                                     1                   5


TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG GTT CGT AAA        101
Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys
        10             15                20


ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG TGC GCT ACT TAC        149
Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
25                 30                 35                 40


AAA CTG TGC CAT CCG GAA GAA CTG GTA CTG CTG GGT CAT TCT CTT GGG        197
Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly
                    45                 50                 55


ATC CCG TGG GCT CCG CTG TCT TCT TGC CCA TCT CAA GCT CTT CAG CTG        245
Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
            60                 65                 70


GCT GGT TGT CTG TCT CAA CTG CAT TCT GGT CTG TTC CTG TAT CAG GGT        293
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
            75                 80                 85


CTT CTG CAA GCT CTG GAA GGT ATC TCT CCG GAA CTG GGT CCG ACT CTG        341
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu
        90                 95                 100


GAC ACT CTG CAG CTA GAT GTA GCT GAC TTT GCT ACT ACT ATT TGG CAA        389
Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
105                 110                115                120


CAG ATG GAA GAG CTC GGT ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT        437
Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
                    125                130                135


GCT ATG CCG GCA TTC GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA        485
Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
            140                145                150


CTG GTT GCT TCT CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT        533
Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val
            155                160                165


CTG CGT CAT CTG GCT CAG CCG TAATAGAATT C                               565
Leu Arg His Leu Ala Gln Pro
        170                175
```

(2) INFORMATION FOR SEQ ID NO:2:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

- 75 -

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1   5   10   15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35   40   45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:3:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 24 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTTTCTGCTG CGTTGTCTGG AACA   24

(2) INFORMATION FOR SEQ ID NO:4:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 23 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single

        (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACAGGTTCGT CGTATCCAGG GTG   23

 (2) INFORMATION FOR SEQ ID NO:5:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 23 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTGCAAGA ACGTCTGTGC GTC   23

 (2) INFORMATION FOR SEQ ID NO:6:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 23 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGCTACTTAC CGTCTGTGCC ATC   23

 (2) INFORMATION FOR SEQ ID NO:7:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 24 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTTCTGCTG CGTTGTCTGG AACA   24

 (2) INFORMATION FOR SEQ ID NO:8:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 23 base pairs

- 77 -

    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

  (ii) MOLECULE TYPE: DNA

  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACAGGTTCGT CGTATCCAGG GTG   23

  (2) INFORMATION FOR SEQ ID NO:9:

    (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 23 base pairs
      (B) TYPE: nucleic acid
      (C) STRANDEDNESS: single
      (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CACTGCAAGA ACGTCTGTGC GCT   23

  (2) INFORMATION FOR SEQ ID NO:10:

    (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 24 base pairs
      (B) TYPE: nucleic acid
      (C) STRANDEDNESS: single
      (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTTTCTGCTG CGTTGTCTGG AACA   24

  (2) INFORMATION FOR SEQ ID NO:11:

    (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 23 base pairs
      (B) TYPE: nucleic acid
      (C) STRANDEDNESS: single
      (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ACAGGTTCGT CGTATCCAGG GTG   23

- 78 -

(2) INFORMATION FOR SEQ ID NO:12:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 23 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: DNA

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGCTACTTAC CGTCTGTCCC ATC   23

(2) INFORMATION FOR SEQ ID NO:13:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 24 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: DNA

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTTCTGCTG CGTTGTCTGG AACA   24

(2) INFORMATION FOR SEQ ID NO:14:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 23 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: DNA

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CACTGCAAGA ACGTCTGTGC GCT   23

(2) INFORMATION FOR SEQ ID NO:15:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 23 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

    CGCTACTTAC CGTCTGTGCC ATC   23

    (2) INFORMATION FOR SEQ ID NO:16:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

         (ii) MOLECULE TYPE: DNA

         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

    ACAGGTTCGT CGTATCCAGG GTG   23

    (2) INFORMATION FOR SEQ ID NO:17:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

         (ii) MOLECULE TYPE: DNA

         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

    CACTGCAAGA ACGTCTGTGC GCT   23

    (2) INFORMATION FOR SEQ ID NO:18:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

         (ii) MOLECULE TYPE: DNA

         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

    CGCTACTTAC CGTCTGTGCC ATC   23

    (2) INFORMATION FOR SEQ ID NO:19:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 24 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

   CTTTCTGCTG CGTTGTCTGG AACA   24

      (2) INFORMATION FOR SEQ ID NO:20:

           (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

          (ii) MOLECULE TYPE: DNA

          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

   ACAGGTTCGT CGTATCCAGG GTG   23

      (2) INFORMATION FOR SEQ ID NO:21:

           (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

          (ii) MOLECULE TYPE: DNA

          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

   CACTGCAAGA ACGTCTGTGC GCT   23

      (2) INFORMATION FOR SEQ ID NO:22:

           (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

          (ii) MOLECULE TYPE: DNA

          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

   CGCTACTTAC CGTCTGTGCC ATC   23

      (2) INFORMATION FOR SEQ ID NO:23:

           (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 23 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single

        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCTGCTGAAA GCTCTGGAAC AGG   23

(2) INFORMATION FOR SEQ ID NO:24:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 23 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CTTGTCCATC TGAAGCTCTT CAG   23

(2) INFORMATION FOR SEQ ID NO:25:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 37 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GAAAAACTGT CCGCTACTTA CAAACTGTCC CATCCGG   37

(2) INFORMATION FOR SEQ ID NO:26:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTCGTAAAAT CGCGGGTGAC GG   22

(2) INFORMATION FOR SEQ ID NO:27:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid

- 82 -

```
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: DNA

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCATCTGGCT GCGCCGTAAT AG                                              22


(2) INFORMATION FOR SEQ ID NO:28:

       (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 22 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: DNA

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CCGTGTTCTG GCTCATCTGG CT                                              22


(2) INFORMATION FOR SEQ ID NO:29:

       (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 24 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: DNA

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GAAGTATCTT ACGCTGTTCT GCGT                                            24


(2) INFORMATION FOR SEQ ID NO:30:

       (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 25 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: DNA

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAAGTATCTT ACTAAGTTCT GCGTC                                           25
```

(2) INFORMATION FOR SEQ ID NO:31:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CGCTACTTAC GCACTGTGCC AT   22

(2) INFORMATION FOR SEQ ID NO:32:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAAACTGTGC AAGCCGGAAG AG   22

(2) INFORMATION FOR SEQ ID NO:33:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CATCCGGAAG CACTGGTACT GC   22

(2) INFORMATION FOR SEQ ID NO:34:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 23 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAACAGGTT GCTAAAATCC AGG   23

- 84 -

(2) INFORMATION FOR SEQ ID NO:35:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 25 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GAACAGGTTC GTGCGATCCA GGGTG   25

(2) INFORMATION FOR SEQ ID NO:36:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GAAATGTCTG GCACAGGTTC GT   22

(2) INFORMATION FOR SEQ ID NO:37:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 19 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCCAGGGTGC CGGTGCTGC   19

(2) INFORMATION FOR SEQ ID NO:38:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 23 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAGAGCTCGG TGAGGCACCA GCT   23

(2) INFORMATION FOR SEQ ID NO:39:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 23 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCAAGGTGC TGAGCCGGCA TTC   23

(2) INFORMATION FOR SEQ ID NO:40:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 20 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGCTCGGTC TGGCACCAGC   20

(2) INFORMATION FOR SEQ ID NO:41:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 21 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAAGGTGCT CTGCCGGCAT T   21

(2) INFORMATION FOR SEQ ID NO:42:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 23 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

- 86 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TCTGCCGCAA GCCTTTCTGC TGA   23
(2) INFORMATION FOR SEQ ID NO:43:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 24 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTCTGCTG GCATGTCTGG AACA   24

(2) INFORMATION FOR SEQ ID NO:44:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 24 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTATTTGGCA AGCGATGGAA GAGC   24

(2) INFORMATION FOR SEQ ID NO:45:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 21 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGATGGAAG CGCTCGGTAT G   21

(2) INFORMATION FOR SEQ ID NO:46:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 20 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

 GAGCTCGGTC TGGCACCAGC   20

    (2) INFORMATION FOR SEQ ID NO:47:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 21 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

 TCAAGGTGCT CTGCCGGCAT T   21

    (2) INFORMATION FOR SEQ ID NO:48:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 22 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

 GAAATGTCTG GCACAGGTTC GT   22

    (2) INFORMATION FOR SEQ ID NO:49:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 19 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

 TTCCGGAGCG CACAGTTTG   19

    (2) INFORMATION FOR SEQ ID NO:50:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 23 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CGAGAAGGCC TCGGGTGTCA AAC   23

(2) INFORMATION FOR SEQ ID NO:51:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 22 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATGCCAAATT GCAGTAGCAA AG   22

(2) INFORMATION FOR SEQ ID NO:52:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 24 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACAACGGTTT AACGTCATCG TTTC   24

(2) INFORMATION FOR SEQ ID NO:53:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 22 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ATCAGCTACT GCTAGCTGCA GA   22
(2) INFORMATION FOR SEQ ID NO:54:

    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 23 base pairs
       (B) TYPE: nucleic acid
       (C) STRANDEDNESS: single
       (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: DNA

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

    TCAGTCGATG ACGATCGACG TCT   23

        (2) INFORMATION FOR SEQ ID NO:55:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 22 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

            (ii) MOLECULE TYPE: DNA

            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

    TTACGAACCG CTTCCAGACA TT   22

        (2) INFORMATION FOR SEQ ID NO:56:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 25 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

            (ii) MOLECULE TYPE: DNA

            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

    TAAAATGCTT GGCGAAGGTC TGTAA   25

    (2) INFORMATION FOR SEQ ID NO:57:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 22 base pairs
                (B) TYPE: nucleic acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear

            (ii) MOLECULE TYPE: DNA

            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

    GTAGCAAATG CAGCTACATC TA   22

    (2) INFORMATION FOR SEQ ID NO:58:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 25 base pairs
                (B) TYPE: nucleic acid

        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CATCATCGTT TACGTCGATG TAGAT   25

(2) INFORMATION FOR SEQ ID NO:59:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 20 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CCAAGAGAAG CACCCAGCAG   20

(2) INFORMATION FOR SEQ ID NO:60:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 22 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

AGGGTTCTCT TCGTGGGTCG TC   22

(2) INFORMATION FOR SEQ ID NO:61:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 20 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CACTGGCGGT GATAATGAGC   20

(2) INFORMATION FOR SEQ ID NO:62:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 19 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTAGGCCAGG CATTACTGG   19

(2) INFORMATION FOR SEQ ID NO:63:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 21 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCACTGGCGG TGATACTGAG C   21

(2) INFORMATION FOR SEQ ID NO:64:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 33 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGCAGAAAGC TTTCCGGCAG AGAAGAAGCA GGA   33

(2) INFORMATION FOR SEQ ID NO:65:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 54 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: DNA

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GCCGCAAAGC TTTCTGCTGA AATGTCTGGA AGAGGTTCGT AAAATCCAGG GTGA   54

- 92 -

(2) INFORMATION FOR SEQ ID NO:66:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 59 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: DNA

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGAATGCA GAAGCAAATG CCGGCATAGC ACCTTCAGTC GGTTGCAGAG CTGGTGCCA   59

(2) INFORMATION FOR SEQ ID NO:67:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 175 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1   5   10   15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
                35   40   45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:68:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
                35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:69:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

- 94 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:70:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

- 95 -

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70                75                80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                90                95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100               105               110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115               120               125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130               135               140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145               150               155               160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165               170               175
```

(2) INFORMATION FOR SEQ ID NO:71:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                 10                15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
                20                25                30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                40                45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                55                60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70                75                80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                90                95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100               105               110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115               120               125
```

- 96 -

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130             135             140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145         ·         150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165             170             175
```

(2) INFORMATION FOR SEQ ID NO:72:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
    1.      .     5               10              15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20              25              30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35              40              45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50              55              60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65              70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115     .       120             125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130             135             140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165             170             175
```

(2) INFORMATION FOR SEQ ID NO:73:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 175 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                   10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:74:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 175 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1               5                   10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80


Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:75:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1               5                   10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:76:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1                   5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
```

- 100 -

```
          115                    120                      125
```

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
```
    130                   135                    140
```

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
```
145                   150                    155                   160
```

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
```
                      165                    170                   175
```

(2) INFORMATION FOR SEQ ID NO:77:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
```
 1               5                    10                   15
```

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
```
                 20                   25                   30
```

Gln Glu Lys Leu Ser Ala Thr Tyr Lys Leu Ser His Pro Glu Glu Leu
```
            35                   40                   45
```

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
```
       50                   55                   60
```

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
```
 65                   70                   75                   80
```

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
```
                  85                   90                   95
```

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
```
            100                  105                  110
```

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
```
        115                  120                  125
```

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
```
    130                  135                  140
```

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
```
145                  150                  155                  160
```

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
```
                      165                  170                  175
```

- 101 -

(2) INFORMATION FOR SEQ ID NO:78:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Ala Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:79:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                  10                  15
```

- 102 -

```
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                    25                30


Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                    40                45


Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                60


Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                75                80


Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                90                    95


Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                   105               110


Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115                   120               125


Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130                   135               140


Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                   150               155               160


Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Ala Pro
                165               170               175
```


(2) INFORMATION FOR SEQ ID NO:80:

            (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 175 amino acids
                (B) TYPE: amino acid
                (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                   10                  15


Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                    25                30


Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                    40                45


Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60


Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                75                80
```

- 103 -

```
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
              85                    90                      95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100                   105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
              115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130                 135 ·               140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Ala His Leu Ala Gln Pro
                  165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:81:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1             5                   10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
              20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                      80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
              85                  90                      95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
              115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130                 135                 140
```

```
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Ala Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:82:

        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 174 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1           5                 10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Val Leu Arg His Leu Ala Gln Pro
                165                 170             174
```

(2) INFORMATION FOR SEQ ID NO:83:

        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 175 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1   5   10   15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Ala Leu Cys His Pro Glu Glu Leu
            35   40   45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:84:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1   5   10   15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Lys Pro Glu Glu Leu
            35   40   45

- 106 -

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                        85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
                115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                        165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:85:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1              5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Ala Leu
            35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                        85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115              120              125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130              135              140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145              150              155              160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165              170              175
```

(2) INFORMATION FOR SEQ ID NO:86:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                10               15

Lys Cys Leu Glu Gln Val Ala Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20               25               30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35               40               45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50               55               60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70               75               80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85               90               95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100              105              110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115              120              125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130              135              140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145              150              155              160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165              170              175
```

- 108 -

(2) INFORMATION FOR SEQ ID NO:87:

         (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 175 amino acids
               (B) TYPE: amino acid
               (D) TOPOLOGY: linear

         (ii) MOLECULE TYPE: protein

         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1   5   10   15

Lys Cys Leu Glu Gln Val Arg Ala Ile Gln Gly Asp Gly Ala Ala Leu
              20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35   40   45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
         50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                  85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
         130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                  165   170   175

(2) INFORMATION FOR SEQ ID NO:88:

         (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 175 amino acids
               (B) TYPE: amino acid
               (D) TOPOLOGY: linear

         (ii) MOLECULE TYPE: protein

- 109 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                   10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:89:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 175 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                   10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

- 110 -

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115             120             125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130             135             140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165             170                 175
```

(2) INFORMATION FOR SEQ ID NO:90:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5              10              15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20              25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35              40              45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50              55              60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Glu Ala
        115             120             125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130             135             140
```

- 111 -

```
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165             170             175
```

(2) INFORMATION FOR SEQ ID NO:91:

        (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 175 amino acids
                (B) TYPE: amino acid
                (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5               10              15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20              25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35              40              45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50              55              60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65             70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115             120             125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Glu Pro Ala Phe Ala Ser Ala
    130             135             140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165             170             175
```

(2) INFORMATION FOR SEQ ID NO:92:

        (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 175 amino acids
                (B) TYPE: amino acid

- 112 -

```
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                   10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:93:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5                   10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30
```

- 113 -

```
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
         35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
         50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
             100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
             115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
         130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                 165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:94:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1               5                   10                  15

Lys Ala Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
             20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
         35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
         50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95
```

- 114 -

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130   135   · 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:95:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1   5   10   15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35   ·   40   45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100   105   110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:96:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
               20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
           35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
       50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
   65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                   85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                  100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
           115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
       130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                  165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:97:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Gly Phe Leu Leu
1               5                   10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30


Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
    65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:98:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1               5                   10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

- 117 -

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
               100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
     130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:99:

         (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 175 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ala Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
               20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
          35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                    85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
               100             105             110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:100:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1             5                 10                 15

Ala Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                 25                 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
          35                 40                 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                 55                 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
  65                 70                 75                 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                 90                 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:101:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
                35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Ala Met Glu Glu Leu Gly Met Ala
                115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
        130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:102:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15
```

- 120 -

```
Lys Cys Leu Glu Ala Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
              20                  25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
          35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
      50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
  65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
              85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
              165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:103:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
              20                  25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Ala Pro Glu Glu Leu
          35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
      50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
  65                  70                  75                  80
```

- 121 -

```
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
              85                  90                      95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                  165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:104:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 175 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5               10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
              20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
          35                  40                  45

Val Leu Leu Gly Ala Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
      50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
              85                  90                      95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
              100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140
```

```
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165             170             175
```

(2) INFORMATION FOR SEQ ID NO:105:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

     (ii) MOLECULE TYPE: protein

     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1             5                 10              15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                40              45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                55                60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                70                75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
            85                90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
        100             105             110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115             120             125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130             135             140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145             150             155             160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165             170             175
```

(2) INFORMATION FOR SEQ ID NO:106:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

- 123 -

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1   5   10   15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35   40   45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50   55   60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65   70   75   80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85   90   95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100   105   110

Ala Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115   120   125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130   135   140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145   150   155   160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165   170   175

(2) INFORMATION FOR SEQ ID NO:107:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1   5   10   15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20   25   30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35   40   45

- 124 -

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50              55              60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
             100              105              110

Asp Phe Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
         115              120              125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
     130              135              140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145              150              155              160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                 165              170              175
```

(2) INFORMATION FOR SEQ ID NO:108:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5              10              15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
             20              25              30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
         35              40              45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50              55              60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65              70              75              80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85              90              95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
             100              105              110
```

- 125 -

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:109:

        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 175 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear

        (ii) MOLECULE TYPE: protein

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Ala Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:110:

      (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 175 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

      (ii) MOLECULE TYPE: protein

      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
                20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Val Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
            115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

WHAT IS CLAIMED IS:

1. A method for preparing a G-CSF analog comprising the steps of:

(a) viewing information conveying the three dimensional structure of a G-CSF molecule;

(b) selecting from said viewed information at least one site on said G-CSF molecule for alteration;

(c) preparing a G-CSF molecule having such alteration; and

(d) optionally, testing such G-CSF molecule for a desired characteristic.

2. A computer based method for preparing a G-CSF analog comprising the steps of:

(a) providing computer expression of the three dimensional structure of a G-CSF molecule;

(b) selecting from said computer expression at least one site on said G-CSF molecule for alteration;

(c) preparing a G-CSF molecule having such alteration; and,

(d) optionally, testing such G-CSF molecule for a desired characteristic.

3. A method for preparing a G-CSF analog with the aid of a computer comprising:

(a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;

(b) viewing said display;

(c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and

- 128 -

     (d) preparing a G-CSF analog with such
alteration.

     4. A computer-based method for preparing a
G-CSF analog comprising the steps of:

5   (a) viewing the three dimensional
structure of a G-CSF molecule via a computer, said
computer having been previously programmed (i) to
express the coordinates of a G-CSF molecule in three
dimensional space, and (ii) to allow for entry of

10 information for alteration of said G-CSF expression and
viewing thereof;

     (b) selecting a site on said visual
image of said G-CSF molecule for alteration;

     (c) entering information for said

15 alteration on said computer;

     (d) viewing a three dimensional
structure of said altered G-CSF molecule via said
computer;

     (e) optionally repeating steps (a)-(e)

20 above;

     (f) preparing a G-CSF analog with said
alteration; and

     (g) optionally testing said G-CSF analog
for a desired characteristic.

25   5. In a computer-based apparatus for
displaying the three dimensional structure of a
molecule, the improvement comprising means for
correlating said three dimensional structure of a G-CSF
molecule with the composition of said G-CSF molecule.

30   6. A method for crystallization of a protein
comprising the steps of:

     (a) combining, optionally by automated
means, aqueous aliquots of said protein with either (i)
aliquots of a salt solution, each aliquot having a

35 different concentration of salt; or (ii) aliquots of a

- 129 -

precipitant solution, each aliquot having a different
concentration of precipitant;

      (b)   selecting at least one of said
combined aliquots, said selection based on the formation
5   of precrystalline forms, or, if no precrystalline forms
are so produced, increasing the protein starting
concentration of said aqueous aliquots of protein and
repeating step (a);

      (c)   after said salt or said precipitant
10 concentration is selected, repeating step (a) with said
previously unselected solution in the presence of said
selected concentration; and,

      (d)   repeating step (b) and step (a)
until a crystal of desired quality is obtained.
15   7.   A method of claim 6 wherein each
combination pursuant to step (a) is performed in a range
of pH.

      8.   A method of claim 6 wherein said combining
of step (a) is done in the presence of a nucleation
20 initiation unit.

      9.   A G-CSF analog having an amino acid
sequence different from that of Figure 1 in that:

      (a)   the N-terminal methionine is
optional; and

25   (b)   one or more of amino acids 58-72 (i)
is substituted with one or more different amino acids or
(ii) deleted; or (iii) chemically modified.

      10. A G-CSF analog of claim 9 wherein said
analog is more resistant to proteolysis than a G-CSF
30 molecule of Figure 1.

      11. A G-CSF analog of claim 10 wherein at
least one of said amino acids is chemically modified by
the addition of a polyethylene glycol molecule.

- 130 -

12. A G-CSF analog having an amino acid sequence different from that of Figure 1 in that:

(a) the N-terminal methionine is optional; and

(b) one or more of amino acids 119-125 (i) is substituted with one or more different amino acids or (ii) deleted; or (iii) chemically modified.

13. A G-CSF analog of claim 12 wherein said analog is more resistant to proteolysis than a G-CSF molecule of Figure 1.

14 A G-CSF analog of claim 12 wherein at least one of said amino acids is chemically modified by the addition of a polyethylene glycol molecule.

15. A G-CSF molecule having the AB loop stabilized by connecting such loop to one or more of helices A, B, C, or D.

16. A G-CSF molecule having the CD loop stabilized by connecting such loop to one or more of helices A, B, C, or D.

17. A G-CSF analog, optionally in a pharmaceutically effective carrier, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17}->Arg^{17}$ and the N-terminal methionine is optional.

18. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{35}->Arg^{35}$ and the N-terminal methionine is optional.

19. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{41}->Arg^{41}$ and the N-terminal methionine is optional.

20. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that

- 131 -

$Lys^{17,24,35}->Arg^{17,24,35}$ and the N-terminal methionine is optional.

21. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,35,41}->Arg^{17,35,41}$ and the N-terminal methionine is optional.

22. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{24,35,41}->Arg^{24,35,41}$ and the N-terminal methionine is optional.

23. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,24,35,41} ->Arg^{17,24,35,41}$ and the N-terminal methionine is optional.

24. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,24,41}->Arg^{17,24,41}$ and the N-terminal methionine is optional.

25. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Gln^{68}->Glu^{68}$ and the N-terminal methionine is optional.

26. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Cys^{37,43}->Ser^{37,43}$ and the N-terminal methionine is optional.

27. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Gln^{26}->Ala^{26}$ and the N-terminal methionine is optional.

- 132 -

28. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Gln^{174}->Ala^{174}$ and the N-terminal methionine is optional.

29. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Arg^{170}->Ala^{170}$ and the N-terminal methionine is optional.

30. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Arg^{167}->Ala^{167}$ and the N-terminal methionine is optional.

31. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
there is a deletion at position 167 and the N-terminal
methionine is optional.

32. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Lys^{41}->Ala^{41}$ and the N-terminal methionine is optional.

33. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$His^{44}->Lys^{44}$ and the N-terminal methionine is optional.

34. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Glu^{47}->Ala^{47}$ and the N-terminal methionine is optional.

35. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Arg^{23}->Ala^{23}$ and the N-terminal methionine is optional.

36. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that

- 133 -

$Lys^{24}->Ala^{24}$ and the N-terminal methionine is optional.

37. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
5    $Glu^{20}->Ala^{20}$ and the N-terminal methionine is optional.

38. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Asp^{28}->Ala^{28}$ and the N-terminal methionine is optional.

10   39. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Met^{127}->Glu^{127}$ and the N-terminal methionine is optional.

40. A G-CSF analog, optionally in a
15   pharmaceutically effective carrier, wherein the amino
acid sequence differs from tha of Figure 1 in that
$Met^{138}->Glu^{138}$ and the N-terminal methionine is optional.

41. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
20   acid sequence differs from that of Figure 1 in that
$Met^{127}->Leu^{127}$ and the N-terminal methionine is optional.

42. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
25   $Met^{138}->Leu^{138}$ and the N-terminal methionine is optional.

43. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Cys^{18}->Ala^{18}$ and the N-terminal methionine is optional.

30   44. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Gln^{12,21}->Glu^{12,21}$ and the N-terminal methionine is
optional.

35   45. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino

acid sequence differs from that of Figure 1 in that
$Gln^{12,21,68} \rightarrow Glu^{12,21,68}$ and the N-terminal methionine is
optional.

     46. A G-CSF analog, optionally in a
5   pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Glu^{20} \rightarrow Ala^{20}$; $Ser^{13} \rightarrow Gly^{13}$ and the N-terminal methionine
is optional.

     47. A G-CSF analog, optionally in a
10   pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Met^{127,138} \rightarrow Leu^{127,138}$ and the N-terminal methionine is
optional.

     48. A G-CSF analog, optionally in a
15   pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Ser^{13} \rightarrow Ala^{13}$ and the N-terminal methionine is optional.

     49. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
20   acid sequence differs from that of Figure 1 in that
$Lys^{17} \rightarrow Ala^{17}$ and the N-terminal methionine is optional.

     50. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
25   $Gln^{121} \rightarrow Ala^{121}$ and the N-terminal methionine is optional.

     51. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$Gln^{21} \rightarrow Ala^{21}$ and the N-terminal methionine is optional.

30   52. A G-CSF analog, optionally in a
pharmaceutically effective carrier, wherein the amino
acid sequence differs from that of Figure 1 in that
$His^{44} \rightarrow Ala^{44}$ and the N-terminal methionine is optional.

     53. A G-CSF analog, optionally in a
35   pharmaceutically effective carrier, wherein said amino
acid sequenc differs from that of Figure 1 in that

- 135 -

His^{53}->Ala^{53} and the N-terminal methionine is optional.

54. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that
5   Asp^{110}->Ala^{110} and the N-terminal methionine is optional.

55. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{113}->Ala^{113} and the N-terminal methionine is optional.
10 56. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Thr^{117}->Ala^{117} and the N-terminal methionine is optional.

57. A G-CSF analog, optionally in a
15 pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{28}->Ala^{28}; Asp^{110} ->Ala^{110} and the N-terminal methionine is optional.

58. A G-CSF analog, optionally in a
20 pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Glu^{124}->Ala^{124} and the N-terminal methionine is optional.

59. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino
25 acid sequence differs from that of Figure 1 in that Phe^{114}->Val^{114}, Thr^{117}->A^{117} and the N-terminal methionine is optional.

FIG.1


```
                                    Met Thr Pro Leu Gly Pro Ala
TCTAGAAAAAACCAAGGAGGTAATAAATA ATG ACT CCA TTA GGT CCT GCT

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
TCT TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG

Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
GTT CGT AAA ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
TGC GCT ACT TAC AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
GGT CAT TCT CTT GGG ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
TCT CAA GCT CTT CAG CTG GCT GGT TGT CTG TCT CAA CTG CAT TCT

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
GGT CTG TTC CTG TAT CAG GGT CTT CTG CAA GCT CTG GAA GGT ATC

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
TCT CCG GAA CTG GGT CCG ACT CTG GAC ACT CTG CAG CTA GAT GTA

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
GCT GAC TTT GCT ACT ACT ATT TGG CAA CAG ATG GAA GAG CTC GGT

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT GCT ATG CCG GCA TTC

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA CTG GTT GCT TCT

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT CTG CGT CAT

Leu Ala Gln Pro OC  AM
CTG GCT CAG CCG TAA TAG AATTC
```

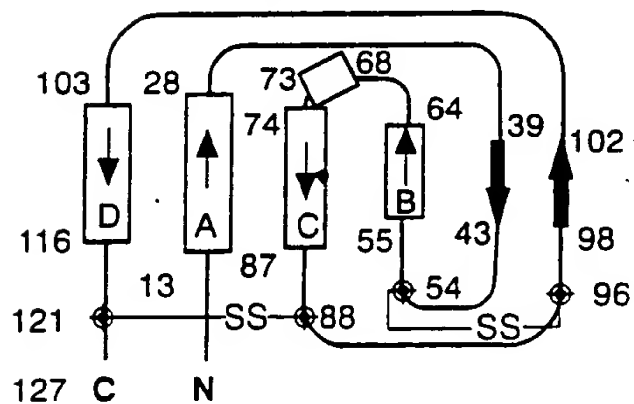**FIG. 2A**
rhG-CSF
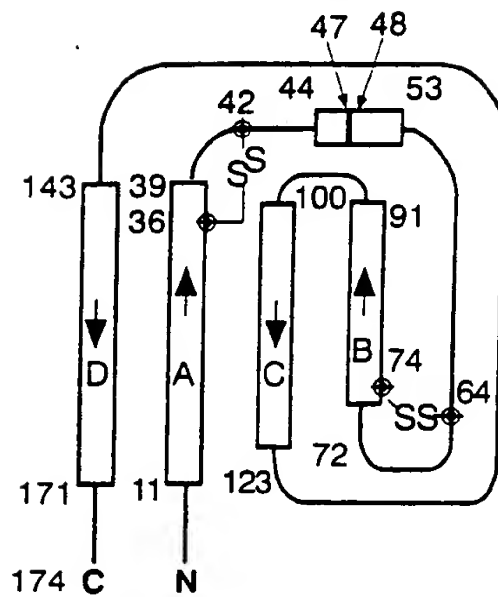
FIG. 2B
hGH
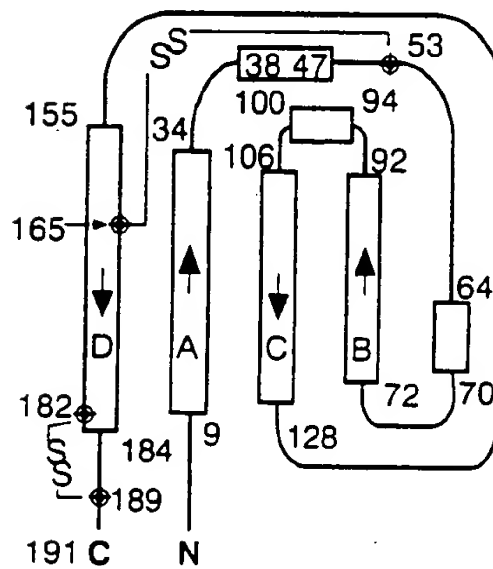
FIG. 2C
pGH
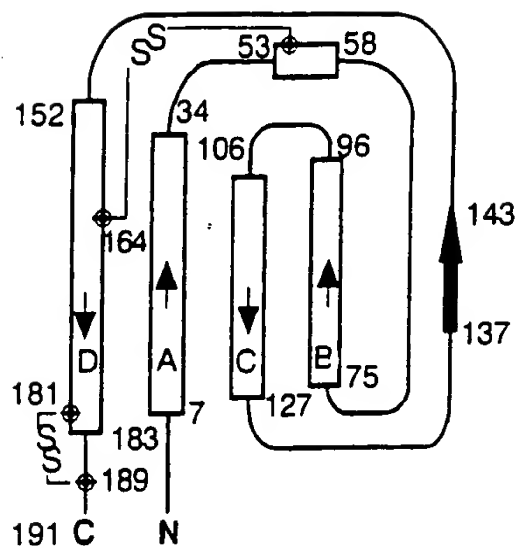
FIG. 2D
GM-CSF

FIG. 2E
INF-B

FIG. 2F
IL-2

FIG. 2G
IL-4

FIG. 3D   FIG. 3C

3_{10}

α

α_L

FIG. 3B   FIG. 3A

FIG.
4AB

FIG.
4D

FIG.
4A

FIG.
4C

47

96

34

113

75

175

119

23

18

1-10
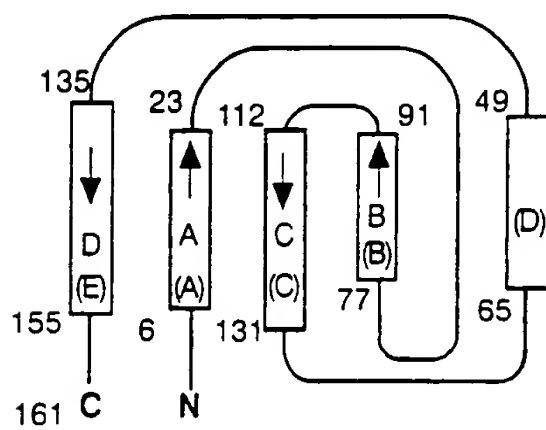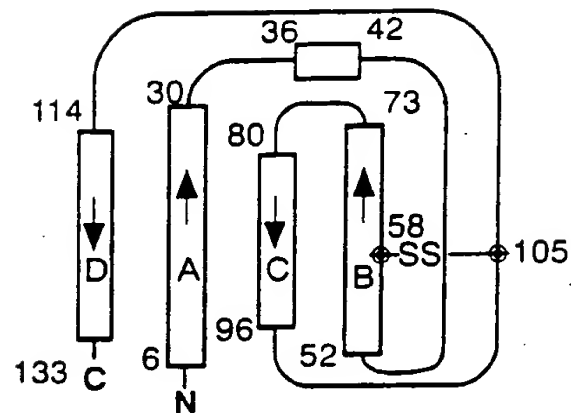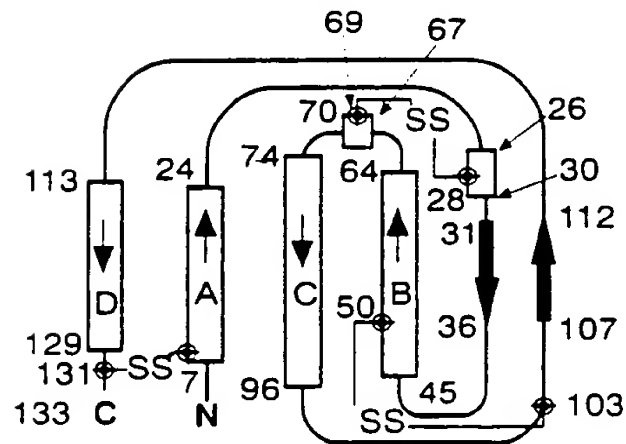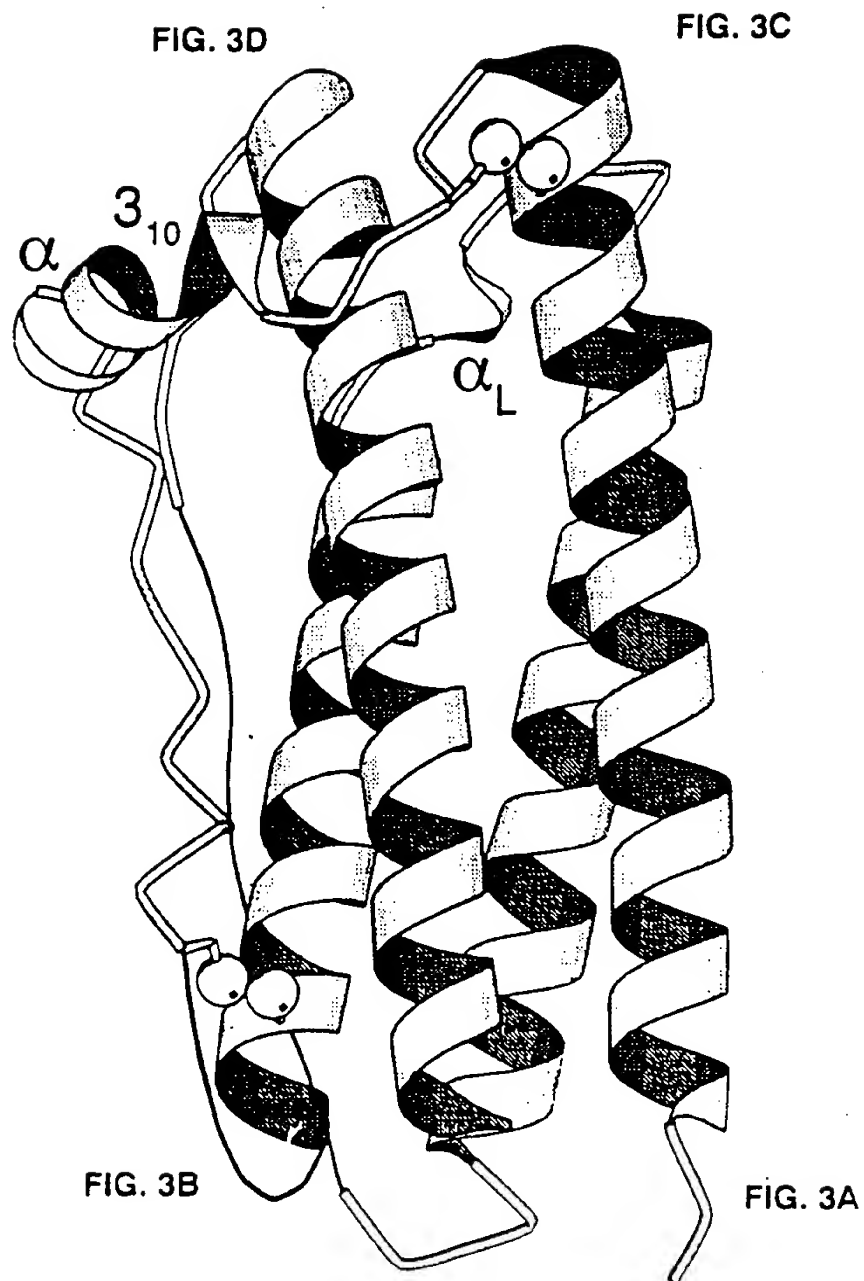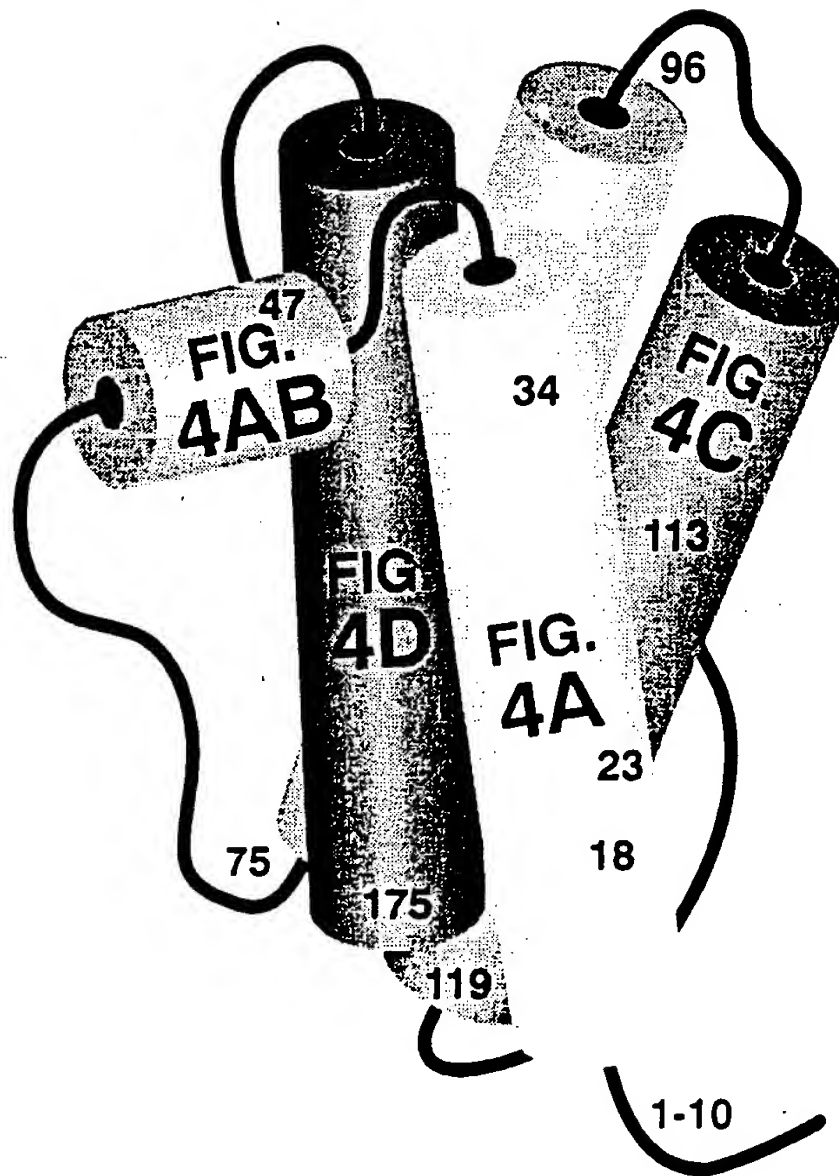
FIG. 5A

ATOM	1	CB	LEU	10	58.751	58.191	-14.868	1.00	61.22	A1
ATOM	2	CG	LEU	10	58.360	59.271	-13.939	1.00	60.19	A1
ATOM	3	CD1	LEU	10	59.307	60.461	-14.022	1.00	60.14	A1
ATOM	4	CD2	LEU	10	56.954	59.658	-14.335	1.00	60.68	A1
ATOM	5	O	LEU	10	60.544	56.734	-13.849	1.00	62.85	A1
ATOM	6	O	LEU	10	60.079	55.595	-14.0a41	1.00	63.08	A1
ATOM	7	HT1	LEU	10	59.876	56.135	-15.998	1.00	0.00	A1
ATOM	8	HT2	LEU	10	61.323	56.887	-16.434	1.00	0.00	A1
ATOM	9	N	LEU	10	60.328	57.059	-16.204	1.00	62.24	A1
ATOM	10	HT3	LEU	10	59.817	57.535	-16.971	1.00	0.00	A1
ATOM	11	CA	LEU	10	60.183	57.758	-14.941	1.00	62.58	A1
ATOM	12	N	PRO	11	61.357	56.962	-12.780	1.00	61.96	A1
ATOM	13	CD	PRO	11	61.960	58.238	-12.383	1.00	61.21	A1
ATOM	14	CA	PRO	11	61.832	55.889	-11.906	1.00	61.34	A1
ATOM	15	CB	PRO	11	62.915	56.547	-11.043	1.00	59.77	A1
ATOM	16	CG	PRO	11	62.511	57.983	-10.975	1.00	59.16	A1
ATOM	17	C	PRO	11	60.712	55.225	-11.109	1.00	60.68	A1
ATOM	18	O	PRO	11	60.075	55.843	-10.250	1.00	61.73	A1
ATOM	19	N	GLN	11	60.466	53.946	-11.407	1.00	59.31	A1
ATOM	20	H	GLN	11	60.944	53.573	-12.175	1.00	0.00	A1
ATOM	21	CA	GLN	12	59.468	53.121	-10.743	1.00	57.22	A1
ATOM	22	CB	GLN	12	59.779	51.646	-10.970	1.00	59.27	A1
ATOM	23	CG	GLN	12	58.620	50.714	-10.591	1.00	59.70	A1
ATOM	24	CD	GLN	12	57.604	50.575	-11.702	1.00	61.71	A1
ATOM	25	OE1	GLN	12	57.170	49.465	-11.970	1.00	65.82	A1
ATOM	26	NE2	GLN	12	57.227	51.534	-12.541	1.00	63.02	A1
ATOM	27	HE21	GLN	12	57.639	52.419	-12.489	1.00	0.00	A1
ATOM	28	HE22	GLN	12	56.500	51.308	-13.156	1.00	0.00	A1
ATOM	29	C	GLN	12	59.336	53.347	-9.245	1.00	55.34	A1
ATOM	30	O	GLN	12	58.242	53.196	-8.708	1.00	54.56	A1
ATOM	31	N	SER	13	60.423	53.732	-8.576	1.00	53.44	A1
ATOM	32	H	SER	13	61.276	53.839	-9.033	1.00	0.00	A1
ATOM	33	CA	SER	13	60.335	53.974	-7.168	1.00	52.86	A1
ATOM	34	CB	SER	13	61.704	54.144	-6.626	1.00	52.24	A1
ATOM	35	OG	SER	13	61.702	53.493	-5.362	1.00	56.64	A1
ATOM	36	HG	SER	13	61.534	52.551	-5.477	1.00	0.00	A1
ATOM	37	C	SER	13	59.497	55.214	-6.900	1.00	52.58	A1
ATOM	38	O	SER	13	58.509	55.144	-6.160	1.00	53.55	A1
ATOM	39	N	PHE	14	59.791	56.333	-7.577	1.00	50.84	A1
ATOM	40	H	PHE	14	60.469	56.292	-8.279	1.00	0.00	A1
ATOM	41	CA	PHE	14	59.067	57.590	-7.423	1.00	47.21	A1
ATOM	42	CB	PHE	14	59.611	58.590	-8.454	1.00	44.68	A1
ATOM	43	CG	PHE	14	58.618	59.669	-8.866	1.00	42.88	A1
ATOM	44	CD1	PHE	14	58.052	59.594	-10.123	1.00	40.40	A1
ATOM	45	CD2	PHE	14	58.264	60.673	-7.978	1.00	40.30	A1
ATOM	46	CE1	PHE	14	57.114	60.518	-10.507	1.00	39.59	A1
ATOM	47	CE2	PHE	14	57.329	61.587	-8.380	1.00	41.82	A1
ATOM	48	CZ	PHE	14	56.751	61.515	-9.635	1.00	41.56	A1
ATOM	49	C	PHE	14	57.605	57.263	-7.661	1.00	45.83	A1
ATOM	50	O	PHE	14	56.789	57.588	-6.805	1.00	46.07	A1
ATOM	51	N	LEU	15	57.298	56.509	-8.718	1.00	44.64	A1
ATOM	52	H	LEU	15	58.024	56.183	-9.287	1.00	0.00	A1
ATOM	53	CA	LEU	15	55.940	56.181	-9.038	1.00	44.53	A1
ATOM	54	CB	LEU	15	55.858	55.402	-10.300	1.00	48.74	A1
ATOM	55	CG	LEU	15	54.853	55.013	-11.289	1.00	51.65	A1
ATOM	56	CD1	LEU	15	55.525	57.121	-12.105	1.00	50.33	A1
ATOM	57	CD2	LEU	15	54.320	54.906	-12.204	1.00	53.77	A1
ATOM	58	C	LEU	15	55.169	55.410	-8.014	1.00	44.07	A1
ATOM	59	O	LEU	15	53.945	55.567	-7.959	1.00	45.46	A1
ATOM	60	N	LEU	16	55.809	54.620	-7.166	1.00	43.18	A1
ATOM	61	H	LEU	16	56.781	54.503	-7.251	1.00	0.00	A1
ATOM	62	CA	LEU	16	55.110	53.913	-6.095	1.00	42.96	A1
ATOM	63	CB	LEU	16	55.866	52.623	-5.751	1.00	43.34	A1
ATOM	64	CG	LEU	16	55.840	51.608	-6.868	1.00	42.25	A1
ATOM	65	CD1	LEU	16	56.889	50.567	-6.596	1.00	43.68	A1
ATOM	66	CD2	LEU	16	54.413	51.068	-7.030	1.00	42.75	A1
ATOM	67	C	LEU	16	54.963	54.778	-4.852	1.00	42.35	A1
ATOM	68	O	LEU	16	54.077	54.579	-4.018	1.00	42.65	A1
ATOM	69	N	LYS	17	55.823	55.779	-4.703	1.00	42.47	A1
ATOM	70	H	LYS	17	56.587	55.840	-5.320	1.00	0.00	A1

FIG.5B

```
ATOM   71 CA  LYS 17   55.681 56.767 -3.650 1.00 42.07 A1
ATOM   72 CB  LYS 17   56.995 57.554 -3.573 1.00 44.14 A1
ATOM   73 CG  LYS 17   57.214 58.197 -2.223 1.00 49.61 A1
ATOM   74 CD  LYS 17   57.114 57.164 -1.086 1.00 55.15 A1
ATOM   75 CE  LYS 17   56.747 57.804  0.293 1.00 62.05 A1
ATOM   76 NZ  LYS 17   55.462 58.533  0.331 1.00 65.43 A1
ATOM   77 HZ1 LYS 17   54.684 57.884  0.098 1.00  0.00 A1
ATOM   78 HZ2 LYS 17   55.482 59.308 -0.362 1.00  0.00 A1
ATOM   79 HZ3 LYS 17   55.312 58.926  1.282 1.00  0.00 A1
ATOM   80 C   LYS 17   54.463 57.640 -4.051 1.00 41.20 A1
ATOM   81 O   LYS 17   53.648 57.999 -3.186 1.00 40.66 A1
ATOM   82 N   CYS 18   54.272 57.992 -5.346 1.00 39.13 A1
ATOM   83 H   CYS 18   54.998 57.809 -5.981 1.00  0.00 A1
ATOM   84 CA  CYS 18   53.080 58.656 -5.802 1.00 37.42 A1
ATOM   85 CB  CYS 18   53.092 58.891 -7.261 1.00 35.02 A1
ATOM   86 SG  CYS 18   54.421 60.026 -7.681 1.00 40.40 A1
ATOM   87 C   CYS 18   51.859 57.789 -5.502 1.00 39.33 A1
ATOM   88 O   CYS 18   50.959 58.346 -4.847 1.00 40.83 A1
ATOM   89 N   LEU 19   51.738 56.475 -5.842 1.00 37.15 A1
ATOM   90 H   LEU 19   52.462 56.038 -6.341 1.00  0.00 A1
ATOM   91 CA  LEU 19   50.521 55.702 -5.534 1.00 36.00 A1
ATOM   92 CB  LEU 19   50.644 54.204 -5.947 1.00 38.31 A1
ATOM   93 CG  LEU 19   49.410 53.271 -5.657 1.00 40.86 A1
ATOM   94 CD1 LEU 19   48.208 53.684 -6.467 1.00 39.71 A1
ATOM   95 CD2 LEU 19   49.692 51.833 -6.113 1.00 45.71 A1
ATOM   96 C   LEU 19   50.102 55.736 -4.076 1.00 33.52 A1
ATOM   97 O   LEU 19   48.930 55.949 -3.766 1.00 32.75 A1
ATOM   98 N   GLU 20   51.030 55.576 -3.166 1.00 31.88 A1
ATOM   99 H   GLU 20   51.940 55.338 -3.455 1.00  0.00 A1
ATOM  100 CA  GLU 20   50.750 55.710 -1.748 1.00 33.40 A1
ATOM  101 CB  GLU 20   52.053 55.334 -1.167 1.00 35.25 A1
ATOM  102 CG  GLU 20   52.508 55.504  0.260 1.00 43.21 A1
ATOM  103 CD  GLU 20   53.948 54.947  0.407 1.00 51.06 A1
ATOM  104 OE1 GLU 20   54.320 54.660  1.546 1.00 56.78 A1
ATOM  105 OE2 GLU 20   54.708 54.766 -0.570 1.00 51.57 A1
ATOM  106 C   GLU 20   50.230 57.117 -1.326 1.00 33.25 A1

ATOM  107 O   GLU 20   49.432 57.291 -0.380 1.00 33.30 A1
ATOM  108 N   GLN 21   50.660 58.167 -2.044 1.00 32.33 A1
ATOM  109 H   GLN 21   51.270 58.004 -2.794 1.00  0.00 A1
ATOM  110 CA  GLN 21   50.275 59.538 -1.742 1.00 31.00 A1
ATOM  111 CB  GLN 21   51.326 60.489 -2.340 1.00 32.37 A1
ATOM  112 CG  GLN 21   52.436 60.530 -1.277 1.00 38.01 A1
ATOM  113 CD  GLN 21   53.622 61.460 -1.504 1.00 42.67 A1
ATOM  114 OE1 GLN 21   54.008 62.236 -0.615 1.00 43.63 A1
ATOM  115 NE2 GLN 21   54.256 61.448 -2.678 1.00 42.31 A1
ATOM  116 HE21 GLN 21  53.965 60.840 -3.384 1.00  0.00 A1
ATOM  117 HE22 GLN 21  55.026 62.052 -2.730 1.00  0.00 A1
ATOM  118 C   GLN 21   48.894 59.765 -2.288 1.00 28.51 A1
ATOM  119 O   GLN 21   48.027 60.242 -1.563 1.00 28.65 A1
ATOM  120 N   VAL 22   48.682 59.319 -3.521 1.00 25.85 A1
ATOM  121 H   VAL 22   49.448 58.980 -4.013 1.00  0.00 A1
ATOM  122 CA  VAL 22   47.382 59.303 -4.161 1.00 24.94 A1
ATOM  123 CB  VAL 22   47.508 58.614 -5.526 1.00 24.09 A1
ATOM  124 CG1 VAL 22   46.154 58.378 -6.096 1.00 19.97 A1
ATOM  125 CG2 VAL 22   48.252 59.479 -6.498 1.00 25.82 A1
ATOM  126 C   VAL 22   46.418 58.549 -3.226 1.00 25.65 A1
ATOM  127 O   VAL 22   45.428 59.190 -2.800 1.00 29.31 A1
ATOM  128 N   ARG 23   46.643 57.291 -2.759 1.00 23.93 A1
ATOM  129 H   ARG 23   47.440 56.819 -3.0?5 1.00  0.00 A1
ATOM  130 CA  ARG 23   45.667 56.593 -1.892 1.00 20.67 A1
ATOM  131 CB  ARG 23   46.104 55.135 -1.635 1.00 20.45 A1
ATOM  132 CG  ARG 23   46.325 54.321 -2.904 1.00 17.51 A1
ATOM  133 CD  ARG 23   45.095 54.446 -3.769 1.00 21.54 A1
ATOM  134 NE  ARG 23   45.076 53.437 -4.809 1.00 24.82 A1
ATOM  135 HE  ARG 23   45.642 52.647 -4.701 1.00  0.00 A1
ATOM  136 CZ  ARG 23   44.323 53.556 -5.904 1.00 27.69 A1
ATOM  137 NH1 ARG 23   43.567 54.669 -6.006 1.00 29.51 A1
ATOM  138 HH11 ARG 23  43.562 55.377 -5.303 1.00  0.00 A1
ATOM  139 HH12 ARG 23  42.956 54.730 -6.789 1.00  0.00 A1
ATOM  140 NH2 ARG 23   44.345 52.604 -6.891 1.00 24.22 A1
ATOM  141 HH21 ARG 23  43.780 52.713 -7.709 1.00  0.00 A1
ATOM  142 HH22 ARG 23  44.936 51.802 -6.793 1.00  0.00 A1
```

FIG.5C

ATOM	143	C	ARG	23	45.458	57.285	-0.560	1.00 20.56	A1
ATOM	144	O	ARG	23	44.374	57.254	0.042	1.00 20.04	A1
ATOM	145	N	LYS	24	46.485	58.015	-0.118	1.00 22.67	A1
ATOM	146	H	LYS	24	47.291	58.105	-0.668	1.00 0.00	A1
ATOM	147	CA	LYS	24	46.431	58.729	1.166	1.00 22.85	A1
ATOM	148	CB	LYS	24	47.811	59.255	1.506	1.00 26.86	A1
ATOM	149	CG	LYS	24	47.821	59.661	2.971	1.00 33.79	A1
ATOM	150	CD	LYS	24	49.121	60.265	3.404	1.00 40.73	A1
ATOM	151	CE	LYS	24	50.258	59.258	3.335	1.00 46.19	A1
ATOM	152	NZ	LYS	24	51.532	59.975	3.333	1.00 51.19	A1
ATOM	153	HZ1	LYS	24	51.637	60.498	4.225	1.00 0.00	A1
ATOM	154	HZ2	LYS	24	51.539	60.651	2.539	1.00 0.00	A1
ATOM	155	HZ3	LYS	24	52.317	59.303	3.216	1.00 0.00	A1
ATOM	156	C	LYS	24	45.455	59.893	1.101	1.00 21.66	A1
ATOM	157	O	LYS	24	44.588	60.068	1.962	1.00 20.90	A1
ATOM	158	N	ILE	25	45.549	60.696	0.044	1.00 21.66	A1
ATOM	159	H	ILE	25	46.242	60.509	-0.629	1.00 0.00	A1
ATOM	160	CA	ILE	25	44.667	61.841	-0.115	1.00 22.53	A1
ATOM	161	CB	ILE	25	45.075	62.694	-1.307	1.00 22.15	A1
ATOM	162	CG2	ILE	25	44.097	63.834	-1.439	1.00 20.44	A1
ATOM	163	CG1	ILE	25	46.475	63.230	-1.136	1.00 21.03	A1
ATOM	164	CD	ILE	25	47.188	63.281	-2.497	1.00 20.03	A1
ATOM	165	C	ILE	25	43.263	61.308	-0.352	1.00 24.75	A1
ATOM	166	O	ILE	25	42.339	61.839	0.301	1.00 26.13	A1
ATOM	167	N	GLN	26	43.065	60.289	-1.244	1.00 22.79	A1
ATOM	168	H	GLN	26	43.842	59.926	-1.726	1.00 0.00	A1
ATOM	169	CA	GLN	26	41.737	59.713	-1.437	1.00 20.12	A1
ATOM	170	CB	GLN	26	41.729	58.539	-2.341	1.00 18.89	A1
ATOM	171	CG	GLN	26	42.203	59.042	-3.627	1.00 19.77	A1
ATOM	172	CD	GLN	26	42.163	57.996	-4.684	1.00 24.26	A1
ATOM	173	OE1	GLN	26	42.550	56.853	-4.465	1.00 24.82	A1
ATOM	174	NE2	GLN	26	41.732	58.351	-5.890	1.00 27.68	A1
ATOM	175	HE21	GLN	26	41.421	59.265	-6.042	1.00 0.00	A1
ATOM	176	HE22	GLN	26	41.743	57.649	-6.552	1.00 0.00	A1
ATOM	177	C	GLN	26	41.207	59.239	-0.111	1.00 21.88	A1
ATOM	178	O	GLN	26	40.067	59.550	0.220	1.00 27.02	A1
ATOM	179	N	GLY	27	41.952	58.622	0.773	1.00 22.54	A1
ATOM	180	H	GLY	27	42.891	58.420	0.576	1.00 0.00	A1
ATOM	181	CA	GLY	27	41.386	58.191	2.037	1.00 25.55	A1
ATOM	182	C	GLY	27	40.936	59.352	2.890	1.00 27.80	A1
ATOM	183	O	GLY	27	39.889	59.251	3.526	1.00 29.95	A1
ATOM	184	N	ASP	28	41.683	60.460	2.915	1.00 29.39	A1
ATOM	185	H	ASP	28	42.547	60.454	2.448	1.00 0.00	A1
ATOM	186	CA	ASP	28	41.257	61.680	3.624	1.00 28.45	A1
ATOM	187	CB	ASP	28	42.266	62.789	3.552	1.00 30.13	A1
ATOM	188	CG	ASP	28	43.737	62.502	3.777	1.00 31.72	A1
ATOM	189	OD1	ASP	28	44.539	63.024	2.995	1.00 31.95	A1
ATOM	190	OD2	ASP	28	44.063	61.811	4.741	1.00 32.00	A1
ATOM	191	C	ASP	28	39.994	62.264	2.960	1.00 25.81	A1
ATOM	192	O	ASP	28	39.101	62.699	3.655	1.00 26.21	A1
ATOM	193	N	GLY	29	39.882	62.270	1.631	1.00 23.93	A1
ATOM	194	H	GLY	29	40.660	61.950	1.135	1.00 0.00	A1
ATOM	195	CA	GLY	29	38.729	62.694	0.886	1.00 25.69	A1
ATOM	196	C	GLY	29	37.528	61.961	1.418	1.00 27.36	A1
ATOM	197	O	GLY	29	36.648	62.558	2.061	1.00 28.14	A1
ATOM	198	N	ALA	30	37.646	60.628	1.295	1.00 27.85	A1
ATOM	199	H	ALA	30	38.442	60.288	0.843	1.00 0.00	A1
ATOM	200	CA	ALA	30	36.683	59.655	1.814	1.00 25.94	A1
ATOM	201	CB	ALA	30	37.269	58.303	1.556	1.00 22.15	A1
ATOM	202	C	ALA	30	36.356	59.842	3.308	1.00 27.18	A1
ATOM	203	O	ALA	30	35.194	59.772	3.754	1.00 28.82	A1
ATOM	204	N	ALA	31	37.340	60.105	4.150	1.00 27.16	A1
ATOM	205	H	ALA	31	38.253	60.114	3.809	1.00 0.00	A1
ATOM	206	CA	ALA	31	37.113	60.470	5.531	1.00 27.70	A1
ATOM	207	CB	ALA	31	38.383	60.881	6.177	1.00 27.65	A1
ATOM	208	C	ALA	31	36.178	61.675	5.660	1.00 30.01	A1
ATOM	209	O	ALA	31	35.195	61.624	6.413	1.00 32.91	A1
ATOM	210	N	LEU	32	36.397	62.744	4.895	1.00 27.63	A1
ATOM	211	H	LEU	32	37.133	62.734	4.242	1.00 0.00	A1
ATOM	212	CA	LEU	32	35.560	63.898	4.997	1.00 28.52	A1
ATOM	213	CB	LEU	32	36.226	65.019	4.167	1.00 32.94	A1
ATOM	214	CG	LEU	32	35.658	66.472	4.091	1.00 32.54	A1

FIG.5D

					x	y	z	occ	B	
ATOM	215	CD1	LEU	32	35.516	67.082	5.499	1.00	32.87	A1
ATOM	216	CD2	LEU	32	36.555	67.267	3.181	1.00	30.97	A1
ATOM	217	C	LEU	32	34.133	63.597	4.518	1.00	27.87	A1
ATOM	218	O	LEU	32	33.169	63.889	5.250	1.00	25.93	A1
ATOM	219	N	GLN	33	33.977	63.028	3.315	1.00	27.51	A1
ATOM	220	H	GLN	33	34.787	62.826	2.802	1.00	0.00	A1
ATOM	221	CA	GLN	33	32.687	62.671	2.775	1.00	30.40	A1
ATOM	222	CB	GLN	33	32.737	61.721	1.614	1.00	29.47	A1
ATOM	223	CG	GLN	33	32.888	62.584	0.436	1.00	29.26	A1
ATOM	224	CD	GLN	33	33.015	61.869	-0.887	1.00	30.21	A1
ATOM	225	OE1	GLN	33	34.064	61.495	-1.452	1.00	29.61	A1
ATOM	226	NE2	GLN	33	31.823	61.759	-1.426	1.00	33.19	A1
ATOM	227	HE21	GLN	33	31.781	61.328	-2.302	1.00	0.00	A1
ATOM	228	HE22	GLN	33	31.042	62.060	-0.914	1.00	0.00	A1
ATOM	229	C	GLN	33	31.839	61.963	3.788	1.00	35.60	A1
ATOM	230	O	GLN	33	30.715	62.416	4.073	1.00	36.49	A1
ATOM	231	N	GLU	34	32.386	60.925	4.438	1.00	39.81	A1
ATOM	232	H	GLU	34	33.340	60.707	4.328	1.00	0.00	A1
ATOM	233	CA	GLU	34	31.541	60.131	5.304	1.00	43.24	A1
ATOM	234	CB	GLU	34	32.228	58.792	5.571	1.00	46.46	A1
ATOM	235	CG	GLU	34	33.274	58.721	6.624	1.00	55.01	A1
ATOM	236	CD	GLU	34	32.777	58.092	7.930	1.00	60.29	A1
ATOM	237	OE1	GLU	34	33.483	57.186	8.412	1.00	63.26	A1
ATOM	238	OE2	GLU	34	31.724	58.504	8.459	1.00	60.44	A1
ATOM	239	C	GLU	34	31.218	60.877	6.564	1.00	43.59	A1
ATOM	240	O	GLU	34	30.175	60.631	7.161	1.00	44.87	A1
ATOM	241	N	LYS	35	32.045	61.811	6.998	1.00	44.80	A1
ATOM	242	H	LYS	35	32.923	61.931	6.569	1.00	0.00	A1
ATOM	243	CA	LYS	35	31.674	62.634	8.134	1.00	45.43	A1
ATOM	244	CB	LYS	35	32.881	63.364	8.686	1.00	47.67	A1
ATOM	245	CG	LYS	35	33.701	62.414	9.510	1.00	52.75	A1
ATOM	246	CD	LYS	35	35.084	63.021	9.548	1.00	57.55	A1
ATOM	247	CE	LYS	35	36.067	62.099	10.238	1.00	60.35	A1
ATOM	248	NZ	LYS	35	35.810	62.064	11.669	1.00	62.91	A1
ATOM	249	HZ1	LYS	35	34.838	61.733	11.840	1.00	0.00	A1
ATOM	250	HZ2	LYS	35	35.930	63.011	12.078	1.00	0.00	A1
ATOM	251	HZ3	LYS	35	36.477	61.405	12.119	1.00	0.00	A1
ATOM	252	C	LYS	35	30.630	63.660	7.697	1.00	44.45	A1
ATOM	253	O	LYS	35	29.730	63.999	8.478	1.00	44.61	A1
ATOM	254	N	LEU	36	30.652	64.190	6.480	1.00	41.21	A1
ATOM	255	H	LEU	36	31.343	63.930	5.836	1.00	0.00	A1
ATOM	256	CA	LEU	36	29.647	65.157	6.144	1.00	40.25	A1
ATOM	257	CB	LEU	36	30.070	65.899	4.889	1.00	39.03	A1
ATOM	258	CG	LEU	36	31.253	66.834	4.935	1.00	39.99	A1
ATOM	259	CD1	LEU	36	31.438	67.404	3.571	1.00	32.08	A1
ATOM	260	CD2	LEU	36	31.034	67.939	5.928	1.00	35.05	A1
ATOM	261	C	LEU	36	28.332	64.414	5.941	1.00	41.90	A1
ATOM	262	O	LEU	36	27.267	64.828	6.431	1.00	42.30	A1
ATOM	263	N	CYS	37	28.392	63.251	5.309	1.00	42.63	A1
ATOM	264	H	CYS	37	29.250	62.904	5.020	1.00	0.00	A1
ATOM	265	CA	CYS	37	27.216	62.469	5.084	1.00	43.53	A1
ATOM	266	C	CYS	37	26.638	62.026	6.362	1.00	44.65	A1
ATOM	267	O	CYS	37	25.426	61.997	6.459	1.00	46.40	A1
ATOM	268	CB	CYS	37	27.474	61.240	4.313	1.00	44.60	A1
ATOM	269	SG	CYS	37	26.133	60.038	4.530	1.00	43.86	A1
ATOM	270	N	ALA	38	27.465	61.734	7.342	1.00	45.96	A1
ATOM	271	H	ALA	38	28.433	61.707	7.202	1.00	0.00	A1
ATOM	272	CA	ALA	38	26.932	61.261	8.592	1.00	48.03	A1
ATOM	273	CB	ALA	38	27.869	60.140	9.108	1.00	48.64	A1
ATOM	274	C	ALA	38	26.748	62.358	9.624	1.00	48.89	A1
ATOM	275	O	ALA	38	26.103	62.085	10.621	1.00	50.72	A1
ATOM	276	N	THR	39	27.256	63.590	9.512	1.00	50.66	A1
ATOM	277	H	THR	39	27.858	63.780	8.770	1.00	0.00	A1
ATOM	278	CA	THR	39	26.976	64.638	10.503	1.00	51.54	A1
ATOM	279	CB	THR	39	28.179	65.593	10.690	1.00	51.76	A1
ATOM	280	OG1	THR	39	29.294	64.826	11.126	1.00	52.65	A1
ATOM	281	HG1	THR	39	29.749	64.481	10.355	1.00	0.00	A1
ATOM	282	CG2	THR	39	27.900	66.655	11.729	1.00	51.62	A1
ATOM	283	C	THR	39	25.775	65.466	10.037	1.00	52.17	A1
ATOM	284	O	THR	39	24.886	65.882	10.781	1.00	52.15	A1
ATOM	285	N	TYR	40	25.751	65.720	8.738	1.00	52.83	A1
ATOM	286	H	TYR	40	26.420	65.331	8.139	1.00	0.00	A1

FIG.5E

```
ATOM  287 CA  TYR 40   24.729 66.561  8.165 1.00 52.53 A1
ATOM  288 CB  TYR 40   25.314 67.872  7.696 1.00 52.15 A1
ATOM  289 CG  TYR 40   26.399 68.458  8.552 1.00 54.11 A1
ATOM  290 CD1 TYR 40   27.678 68.341  8.062 1.00 56.50 A1
ATOM  291 CE1 TYR 40   28.719 68.934  8.724 1.00 58.28 A1
ATOM  292 CD2 TYR 40   26.122 69.144  9.714 1.00 54.86 A1
ATOM  293 CE2 TYR 40   27.170 69.746 10.378 1.00 56.20 A1
ATOM  294 CZ  TYR 40   28.453 69.642  9.872 1.00 58.26 A1
ATOM  295 OH  TYR 40   29.513 70.310 10.463 1.00 61.00 A1
ATOM  296 HH  TYR 40   30.179 70.443  9.782 1.00  0.00 A1
ATOM  297 C   TYR 40   24.035 65.911  6.981 1.00 51.75 A1
ATOM  298 O   TYR 40   23.662 66.578  6.024 1.00 52.52 A1
ATOM  299 N   LYS 41   23.941 64.600  6.965 1.00 50.54 A1
ATOM  300 H   LYS 41   24.474 64.064  7.583 1.00  0.00 A1
ATOM  301 CA  LYS 41   23.112 63.885  6.029 1.00 50.48 A1
ATOM  302 CB  LYS 41   21.641 63.989  6.540 1.00 50.62 A1
ATOM  303 CG  LYS 41   21.387 63.326  7.911 1.00 52.11 A1
ATOM  304 CD  LYS 41   20.112 63.878  8.574 1.00 55.54 A1
ATOM  305 CE  LYS 41   19.578 63.087  9.820 1.00 58.79 A1
ATOM  306 NZ  LYS 41   18.374 63.648 10.457 1.00 58.31 A1
ATOM  307 HZ1 LYS 41   17.605 63.688  9.757 1.00  0.00 A1
ATOM  308 HZ2 LYS 41   18.578 64.607 10.803 1.00  0.00 A1
ATOM  309 HZ3 LYS 41   18.084 63.043 11.252 1.00  0.00 A1
ATOM  310 C   LYS 41   23.251 64.318  4.588 1.00 49.92 A1
ATOM  311 O   LYS 41   22.312 64.124  3.793 1.00 51.49 A1
ATOM  312 N   LEU 42   24.432 64.893  4.246 1.00 48.28 A1
ATOM  313 H   LEU 42   25.103 65.050  4.937 1.00  0.00 A1
ATOM  314 CA  LEU 42   24.742 65.286  2.859 1.00 46.61 A1
ATOM  315 CB  LEU 42   25.565 66.574  2.757 1.00 44.69 A1
ATOM  316 CG  LEU 42   24.807 67.802  3.218 1.00 42.63 A1
ATOM  317 CD1 LEU 42   25.718 68.580  4.097 1.00 43.29 A1
ATOM  318 CD2 LEU 42   24.283 68.590  2.045 1.00 41.26 A1
ATOM  319 C   LEU 42   25.580 64.124  2.397 1.00 45.46 A1
ATOM  320 O   LEU 42   26.766 64.017  2.711 1.00 46.32 A1
ATOM  321 N   CYS 43   24.882 63.193  1.754 1.00 44.09 A1
ATOM  322 H   CYS 43   23.925 63.353  1.619 1.00  0.00 A1
ATOM  323 CA  CYS 43   25.480 61.951  1.358 1.00 42.87 A1
ATOM  324 C   CYS 43   25.448 61.846 -0.123 1.00 41.62 A1
ATOM  325 O   CYS 43   25.762 60.805 -0.666 1.00 41.99 A1
ATOM  326 CB  CYS 43   24.716 60.796  2.026 1.00 41.77 A1
ATOM  327 SG  CYS 43   24.523 61.011  3.835 1.00 45.91 A1
ATOM  328 N   HIS 44   25.057 62.846 -0.882 1.00 42.90 A1
ATOM  329 H   HIS 44   24.841 63.721 -0.491 1.00  0.00 A1
ATOM  330 CA  HIS 44   25.069 62.680 -2.320 1.00 44.60 A1
ATOM  331 CB  HIS 44   23.653 62.264 -2.825 1.00 48.40 A1
ATOM  332 CG  HIS 44   23.085 60.935 -2.310 1.00 50.37 A1
ATOM  333 CD2 HIS 44   22.178 60.844 -1.272 1.00 50.52 A1
ATOM  334 ND1 HIS 44   23.358 59.689 -2.713 1.00 52.28 A1
ATOM  335 HD1 HIS 44   24.130 59.394 -3.251 1.00  0.00 A1
ATOM  336 CE1 HIS 44   22.652 58.873 -1.955 1.00 51.92 A1
ATOM  337 NE2 HIS 44   21.947 59.565 -1.091 1.00 50.53 A1
ATOM  338 HE2 HIS 44   21.290 59.189 -0.466 1.00  0.00 A1
ATOM  339 C   HIS 44   25.522 63.941 -3.047 1.00 43.69 A1
ATOM  340 O   HIS 44   24.765 64.906 -3.108 1.00 43.00 A1
ATOM  341 N   PRO 45   26.710 63.978 -3.667 1.00 43.07 A1
ATOM  342 CD  PRO 45   27.785 62.995 -3.501 1.00 42.17 A1
ATOM  343 CA  PRO 45   27.133 65.024 -4.570 1.00 42.50 A1
ATOM  344 CB  PRO 45   28.380 64.466 -5.217 1.00 39.76 A1
ATOM  345 CG  PRO 45   28.995 63.680 -4.123 1.00 39.09 A1
ATOM  346 C   PRO 45   26.071 65.423 -5.585 1.00 44.49 A1
ATOM  347 O   PRO 45   25.876 66.612 -5.801 1.00 45.36 A1
ATOM  348 N   GLU 46   25.334 64.501 -6.225 1.00 45.36 A1
ATOM  349 H   GLU 46   25.464 63.561 -5.996 1.00  0.00 A1
ATOM  350 CA  GLU 46   24.406 64.806 -7.319 1.00 45.46 A1
ATOM  351 CB  GLU 46   23.952 63.515 -7.997 1.00 50.54 A1
ATOM  352 CG  GLU 46   24.462 63.460 -9.445 1.00 58.48 A1
ATOM  353 CD  GLU 46   23.637 64.215 -10.502 1.00 64.93 A1
ATOM  354 OE1 GLU 46   23.642 65.455 -10.516 1.00 68.55 A1
ATOM  355 OE2 GLU 46   22.995 63.554 -11.332 1.00 68.31 A1
ATOM  356 C   GLU 46   23.181 65.584 -6.937 1.00 42.96 A1
ATOM  357 O   GLU 46   22.532 66.223 -7.748 1.00 41.71 A1
ATOM  358 N   GLU 47   22.919 65.563 -5.654 1.00 41.96 A1
```

```
ATOM  359 H   GLU  47   23.507 65.098  -5.028 1.00  0.00 A1
ATOM  360 CA  GLU  47   21.818 66.301  -5.144 1.00 43.21 A1
ATOM  361 CB  GLU  47   21.294 65.487  -3.963 1.00 43.24 A1
ATOM  362 CG  GLU  47   21.409 65.925  -2.515 1.00 46.07 A1
ATOM  363 CD  GLU  47   20.812 64.907  -1.547 1.00 47.86 A1
ATOM  364 OE1 GLU  47   19.847 64.225  -1.910 1.00 50.99 A1
ATOM  365 OE2 GLU  47   21.313 64.780  -0.427 1.00 49.47 A1
ATOM  366 C   GLU  47   22.295 67.718  -4.809 1.00 44.04 A1
ATOM  367 O   GLU  47   21.532 68.547  -4.292 1.00 44.60 A1
ATOM  368 N   LEU  48   23.567 68.015  -5.121 1.00 43.05 A1
ATOM  369 H   LEU  48   24.140 67.310  -5.465 1.00  0.00 A1
ATOM  370 CA  LEU  48   24.166 69.318  -4.904 1.00 42.42 A1
ATOM  371 CB  LEU  48   25.223 69.201  -3.858 1.00 40.53 A1
ATOM  372 CG  LEU  48   24.920 68.695  -2.489 1.00 41.87 A1
ATOM  373 CD1 LEU  48   26.277 68.424  -1.892 1.00 41.71 A1
ATOM  374 CD2 LEU  48   24.096 69.670  -1.633 1.00 41.13 A1
ATOM  375 C   LEU  48   24.792 69.937  -6.166 1.00 42.37 A1
ATOM  376 O   LEU  48   25.439 70.994  -6.098 1.00 42.37 A1
ATOM  377 N   VAL  49   24.566 69.366  -7.347 1.00 41.52 A1
ATOM  378 H   VAL  49   23.951 68.602  -7.362 1.00  0.00 A1
ATOM  379 CA  VAL  49   25.191 69.822  -8.578 1.00 43.34 A1
ATOM  380 CB  VAL  49   24.890 68.761  -9.636 1.00 44.29 A1
ATOM  381 CG1 VAL  49   23.381 68.709  -9.830 1.00 47.50 A1
ATOM  382 CG2 VAL  49   25.540 69.086 -10.975 1.00 45.25 A1
ATOM  383 C   VAL  49   24.740 71.214  -9.028 1.00 44.98 A1
ATOM  384 O   VAL  49   25.401 71.901  -9.814 1.00 46.03 A1
ATOM  385 N   LEU  50   23.565 71.602  -8.530 1.00 46.16 A1
ATOM  386 H   LEU  50   23.081 70.933  -8.006 1.00  0.00 A1
ATOM  387 CA  LEU  50   22.908 72.895  -8.729 1.00 46.03 A1
ATOM  388 CB  LEU  50   21.469 72.769  -8.264 1.00 46.43 A1
ATOM  389 CG  LEU  50   20.443 73.718  -8.760 1.00 44.16 A1
ATOM  390 CD1 LEU  50   20.259 73.558 -10.243 1.00 44.79 A1
ATOM  391 CD2 LEU  50   19.159 73.400  -8.079 1.00 44.66 A1
ATOM  392 C   LEU  50   23.632 73.968  -7.917 1.00 45.85 A1
ATOM  393 O   LEU  50   23.996 74.989  -8.484 1.00 44.52 A1
ATOM  394 N   LEU  51   23.853 73.764  -6.606 1.00 45.44 A1

ATOM  395 H   LEU  51   23.489 72.958  -6.189 1.00  0.00 A1
ATOM  396 CA  LEU  51   24.676 74.656  -5.805 1.00 46.04 A1
ATOM  397 CB  LEU  51   24.860 74.084  -4.435 1.00 45.53 A1
ATOM  398 CG  LEU  51   25.741 74.931  -3.535 1.00 47.78 A1
ATOM  399 CD1 LEU  51   25.148 76.320  -3.322 1.00 47.13 A1
ATOM  400 CD2 LEU  51   25.902 74.202  -2.219 1.00 48.33 A1
ATOM  401 C   LEU  51   26.064 74.845  -6.436 1.00 46.27 A1
ATOM  402 O   LEU  51   26.551 75.966  -6.612 1.00 47.62 A1
ATOM  403 N   GLY  52   26.702 73.736  -6.809 1.00 44.84 A1
ATOM  404 H   GLY  52   26.306 72.869  -6.578 1.00  0.00 A1
ATOM  405 CA  GLY  52   27.989 73.758  -7.453 1.00 42.91 A1
ATOM  406 C   GLY  52   27.984 74.533  -8.750 1.00 42.47 A1
ATOM  407 O   GLY  52   28.853 75.364  -8.983 1.00 42.06 A1
ATOM  408 N   HIS  53   27.047 74.307  -9.653 1.00 42.02 A1
ATOM  409 H   HIS  53   26.366 73.624  -9.471 1.00  0.00 A1
ATOM  410 CA  HIS  53   27.009 75.104 -10.861 1.00 42.23 A1
ATOM  411 CB  HIS  53   25.842 74.689 -11.706 1.00 42.21 A1
ATOM  412 CG  HIS  53   26.076 73.399 -12.460 1.00 44.60 A1
ATOM  413 CD2 HIS  53   25.112 72.774 -13.200 1.00 47.49 A1
ATOM  414 ND1 HIS  53   27.180 72.669 -12.578 1.00 46.76 A1
ATOM  415 HD1 HIS  53   28.039 72.853 -12.139 1.00  0.00 A1
ATOM  416 CE1 HIS  53   26.954 71.641 -13.346 1.00 46.90 A1
ATOM  417 NE2 HIS  53   25.704 71.725 -13.707 1.00 50.22 A1
ATOM  418 HE2 HIS  53   25.237 71.033 -14.239 1.00  0.00 A1
ATOM  419 C   HIS  53   26.893 76.585 -10.536 1.00 42.72 A1
ATOM  420 O   HIS  53   27.622 77.399 -11.068 1.00 42.03 A1
ATOM  421 N   SER  54   26.099 76.920  -9.535 1.00 45.08 A1
ATOM  422 H   SER  54   25.673 76.218  -9.001 1.00  0.00 A1
ATOM  423 CA  SER  54   25.792 78.278  -9.177 1.00 46.92 A1
ATOM  424 CB  SER  54   24.576 78.181  -8.289 1.00 48.86 A1
ATOM  425 OG  SER  54   23.521 77.616  -9.112 1.00 53.06 A1
ATOM  426 HG  SER  54   23.465 76.677  -8.918 1.00  0.00 A1
ATOM  427 C   SER  54   26.939 79.033  -8.549 1.00 47.92 A1
ATOM  428 O   SER  54   27.038 80.264  -8.655 1.00 49.60 A1
ATOM  429 N   LEU  55   27.837 78.273  -7.933 1.00 47.59 A1
ATOM  430 H   LEU  55   27.638 77.322  -7.791 1.00  0.00 A1
```

FIG. 5F

FIG. 56

```
ATOM  431 CA  LEU 55  29.075 78.810  -7.401 1.00 45.27 A1
ATOM  432 CB  LEU 55  29.552 77.913  -6.243 1.00 45.49 A1
ATOM  433 CG  LEU 55  28.840 77.992  -4.874 1.00 47.30 A1
ATOM  434 CD1 LEU 55  28.876 76.596  -4.299 1.00 49.52 A1
ATOM  435 CD2 LEU 55  29.530 78.921  -3.862 1.00 45.69 A1
ATOM  436 C   LEU 55  30.133 78.889  -8.492 1.00 43.63 A1
ATOM  437 O   LEU 55  31.247 79.350  -8.272 1.00 43.24 A1
ATOM  438 N   GLY 56  29.855 78.383  -9.675 1.00 43.55 A1
ATOM  439 H   GLY 56  28.984 77.975  -9.828 1.00  0.00 A1
ATOM  440 CA  GLY 56  30.814 78.390 -10.753 1.00 45.59 A1
ATOM  441 C   GLY 56  32.182 77.811 -10.392 1.00 46.76 A1
ATOM  442 O   GLY 56  33.171 78.213 -11.015 1.00 47.31 A1
ATOM  443 N   ILE 57  32.247 76.885  -9.412 1.00 47.49 A1
ATOM  444 H   ILE 57  31.392 76.594  -9.042 1.00  0.00 A1
ATOM  445 CA  ILE 57  33.486 76.249  -8.950 1.00 48.28 A1
ATOM  446 CB  ILE 57  33.144 75.172  -7.863 1.00 47.79 A1
ATOM  447 CG2 ILE 57  34.457 74.591  -7.348 1.00 46.85 A1
ATOM  448 CG1 ILE 57  32.338 75.764  -6.701 1.00 45.09 A1
ATOM  449 CD  ILE 57  31.859 74.739  -5.659 1.00 41.23 A1
ATOM  450 C   ILE 57  34.276 75.602 -10.115 1.00 49.15 A1
ATOM  451 O   ILE 57  33.678 74.935 -10.968 1.00 49.04 A1
ATOM  452 N   PRO 58  35.596 75.817 -10.248 1.00 49.75 A1
ATOM  453 CD  PRO 58  36.402 76.743  -9.433 1.00 50.94 A1
ATOM  454 CA  PRO 58  36.421 75.228 -11.302 1.00 50.72 A1
ATOM  455 CB  PRO 58  37.525 76.241 -11.488 1.00 50.92 A1
ATOM  456 CG  PRO 58  37.814 76.663 -10.041 1.00 50.82 A1
ATOM  457 C   PRO 58  36.916 73.845 -10.875 1.00 50.36 A1
ATOM  458 O   PRO 58  37.187 73.599  -9.691 1.00 49.75 A1
ATOM  459 N   TRP 59  37.030 72.927 -11.816 1.00 50.37 A1
ATOM  460 H   TRP 59  36.888 73.141 -12.760 1.00  0.00 A1
ATOM  461 CA  TRP 59  37.524 71.595 -11.482 1.00 51.78 A1
ATOM  462 CB  TRP 59  36.435 70.562 -11.857 1.00 49.06 A1
ATOM  463 CG  TRP 59  35.254 70.712 -10.889 1.00 46.37 A1
ATOM  464 CD2 TRP 59  35.320 70.845  -9.521 1.00 44.06 A1
ATOM  465 CE2 TRP 59  33.998 71.027  -9.205 1.00 44.18 A1
ATOM  466 CE3 TRP 59  36.274 70.842  -8.538 1.00 44.03 A1
ATOM  467 CD1 TRP 59  33.972 70.794 -11.354 1.00 45.17 A1
ATOM  468 NE1 TRP 59  33.229 70.994 -10.297 1.00 43.17 A1
ATOM  469 HE1 TRP 59  32.301 71.312 -10.332 1.00  0.00 A1
ATOM  470 CZ2 TRP 59  33.598 71.215  -7.916 1.00 45.60 A1
ATOM  471 CZ3 TRP 59  35.893 71.028  -7.243 1.00 45.25 A1
ATOM  472 CH2 TRP 59  34.565 71.214  -6.938 1.00 46.43 A1
ATOM  473 C   TRP 59  38.815 71.435 -12.256 1.00 52.84 A1
ATOM  474 O   TRP 59  38.842 71.972 -13.372 1.00 54.96 A1
ATOM  475 N   ALA 60  39.912 70.834 -11.777 1.00 51.97 A1
ATOM  476 H   ALA 60  39.857 70.269 -10.977 1.00  0.00 A1
ATOM  477 CA  ALA 60  41.108 70.870 -12.609 1.00 52.18 A1
ATOM  478 CB  ALA 60  42.303 70.610 -11.748 1.00 51.75 A1
ATOM  479 C   ALA 60  41.055 69.857 -13.746 1.00 52.16 A1
ATOM  480 O   ALA 60  40.545 68.760 -13.530 1.00 52.17 A1
ATOM  481 N   PRO 61  41.435 70.145 -14.986 1.00 53.34 A1
ATOM  482 CD  PRO 61  41.370 71.458 -15.622 1.00 54.76 A1
ATOM  483 CA  PRO 61  41.691 69.145 -15.993 1.00 55.57 A1
ATOM  484 CB  PRO 61  41.792 69.918 -17.310 1.00 54.95 A1
ATOM  485 CG  PRO 61  42.211 71.297 -16.901 1.00 54.05 A1
ATOM  486 C   PRO 61  42.934 68.333 -15.690 1.00 57.54 A1
ATOM  487 O   PRO 61  43.757 68.661 -14.834 1.00 57.20 A1
ATOM  488 N   LEU 62  43.040 67.271 -16.486 1.00 59.98 A1
ATOM  489 H   LEU 62  42.285 67.067 -17.077 1.00  0.00 A1
ATOM  490 CA  LEU 62  44.184 66.370 -16.471 1.00 63.64 A1
ATOM  491 CB  LEU 62  44.062 65.417 -15.260 1.00 63.72 A1
ATOM  492 CG  LEU 62  45.323 64.691 -14.865 1.00 64.43 A1
ATOM  493 CD1 LEU 62  46.394 65.704 -14.488 1.00 64.02 A1
ATOM  494 CD2 LEU 62  45.016 63.764 -13.717 1.00 64.98 A1
ATOM  495 C   LEU 62  44.214 65.611 -17.812 1.00 65.69 A1
ATOM  496 OT1 LEU 62  44.256 66.302 -18.844 1.00 68.47 A1
ATOM  497 OT2 LEU 62  44.194 64.371 -17.845 1.00 66.57 A1
ATOM  498 CB  LEU 72  57.448 63.159 -19.422 1.00 63.44 A2
ATOM  499 CG  LEU 72  57.716 62.495 -18.117 1.00 63.40 A2
ATOM  500 CD1 LEU 72  56.719 61.408 -17.913 1.00 61.50 A2
ATOM  501 CD2 LEU 72  59.107 61.901 -18.121 1.00 63.22 A2
ATOM  502 C   LEU 72  55.897 65.084 -18.876 1.00 65.40 A2
```

FIG. 5H

```
ATOM   503   O    LEU  72   54.827 65.301 -18.316 1.00 67.30   A2
ATOM   504   HT1  LEU  72   56.469 64.683 -21.261 1.00  0.00   A2
ATOM   505   HT2  LEU  72   54.827 64.355 -20.951 1.00  0.00   A2
ATOM   506   N    LEU  72   55.795 63.983 -20.899 1.00 66.29   A2
ATOM   507   HT3  LEU  72   55.866 63.098 -21.439 1.00  0.00   A2
ATOM   508   CA   LEU  72   56.064 63.714 -19.512 1.00 64.91   A2
ATOM   509   N    ALA  73   56.807 66.046 -19.086 1.00 64.54   A2
ATOM   510   H    ALA  73   57.690 65.804 -19.432 1.00  0.00   A2
ATOM   511   CA   ALA  73   56.707 67.433 -18.615 1.00 62.55   A2
ATOM   512   CB   ALA  73   57.553 68.314 -19.529 1.00 64.84   A2
ATOM   513   C    ALA  73   55.319 68.024 -18.539 1.00 60.37   A2
ATOM   514   O    ALA  73   54.801 68.180 -17.456 1.00 59.42   A2
ATOM   515   N    GLY  74   54.693 68.226 -19.691 1.00 59.72   A2
ATOM   516   H    GLY  74   55.212 68.174 -20.514 1.00  0.00   A2
ATOM   517   CA   GLY  74   53.336 68.728 -19.816 1.00 59.99   A2
ATOM   518   C    GLY  74   52.327 68.114 -18.865 1.00 60.27   A2
ATOM   519   O    GLY  74   51.880 68.796 -17.935 1.00 60.80   A2
ATOM   520   N    CYS  75   51.945 66.850 -19.030 1.00 59.60   A2
ATOM   521   H    CYS  75   52.160 66.358 -19.839 1.00  0.00   A2
ATOM   522   CA   CYS  75   51.002 66.276 -18.078 1.00 60.17   A2
ATOM   523   CB   CYS  75   50.670 64.801 -18.464 1.00 64.08   A2
ATOM   524   SG   CYS  75   49.832 64.732 -20.096 1.00 73.47   A2
ATOM   525   C    CYS  75   51.502 66.346 -16.642 1.00 56.73   A2
ATOM   526   O    CYS  75   50.734 66.748 -15.765 1.00 55.82   A2
ATOM   527   N    LEU  76   52.795 66.142 -16.396 1.00 53.93   A2
ATOM   528   H    LEU  76   53.423 66.043 -17.137 1.00  0.00   A2
ATOM   529   CA   LEU  76   53.325 66.156 -15.044 1.00 52.94   A2
ATOM   530   CB   LEU  76   54.798 65.754 -15.181 1.00 50.81   A2
ATOM   531   CG   LEU  76   55.575 65.011 -14.090 1.00 49.02   A2
ATOM   532   CD1  LEU  76   54.852 63.740 -13.698 1.00 46.76   A2
ATOM   533   CD2  LEU  76   56.951 64.633 -14.623 1.00 47.67   A2
ATOM   534   C    LEU  76   53.093 67.545 -14.425 1.00 53.65   A2
ATOM   535   O    LEU  76   52.731 67.716 -13.244 1.00 53.50   A2
ATOM   536   N    SER  77   53.137 68.553 -15.301 1.00 53.91   A2
ATOM   537   H    SER  77   53.322 68.361 -16.242 1.00  0.00   A2
ATOM   538   CA   SER  77   52.882 69.932 -14.942 1.00 54.93   A2
ATOM   539   CB   SER  77   53.425 70.835 -16.040 1.00 58.32   A2
ATOM   540   OG   SER  77   54.806 70.587 -16.310 1.00 63.35   A2
ATOM   541   HG   SER  77   54.949 69.637 -16.315 1.00  0.00   A2
ATOM   542   C    SER  77   51.382 70.172 -14.759 1.00 53.47   A2
ATOM   543   O    SER  77   50.982 70.965 -13.899 1.00 53.54   A2
ATOM   544   N    GLN  78   50.509 69.501 -15.512 1.00 51.82   A2
ATOM   545   H    GLN  78   50.857 68.901 -16.207 1.00  0.00   A2
ATOM   546   CA   GLN  78   49.074 69.619 -15.349 1.00 50.74   A2
ATOM   547   CB   GLN  78   48.402 68.877 -16.451 1.00 54.31   A2
ATOM   548   CG   GLN  78   47.420 69.784 -17.160 1.00 58.59   A2
ATOM   549   CD   GLN  78   46.557 68.940 -18.071 1.00 62.32   A2
ATOM   550   OE1  GLN  78   47.005 68.260 -18.998 1.00 65.94   A2
ATOM   551   NE2  GLN  78   45.269 68.889 -17.800 1.00 63.17   A2
ATOM   552   HE21 GLN  78   44.973 69.327 -16.972 1.00  0.00   A2
ATOM   553   HE22 GLN  78   44.704 68.444 -18.456 1.00  0.00   A2
ATOM   554   C    GLN  78   48.591 69.065 -14.011 1.00 48.17   A2
ATOM   555   O    GLN  78   47.691 69.618 -13.368 1.00 46.31   A2
ATOM   556   N    LEU  79   49.236 67.988 -13.564 1.00 45.89   A2
ATOM   557   H    LEU  79   49.920 67.584 -14.140 1.00  0.00   A2
ATOM   558   CA   LEU  79   48.919 67.359 -12.294 1.00 44.54   A2
ATOM   559   CB   LEU  79   49.617 66.015 -12.259 1.00 45.06   A2
ATOM   560   CG   LEU  79   49.154 64.895 -11.351 1.00 45.18   A2
ATOM   561   CD1  LEU  79   49.634 63.594 -11.957 1.00 48.06   A2
ATOM   562   CD2  LEU  79   49.766 64.986  -9.969 1.00 46.03   A2
ATOM   563   C    LEU  79   49.366 68.265 -11.170 1.00 43.49   A2
ATOM   564   O    LEU  79   48.645 68.509 -10.199 1.00 43.20   A2
ATOM   565   N    HIS  80   50.556 68.834 -11.329 1.00 43.83   A2
ATOM   566   H    HIS  80   51.115 68.548 -12.085 1.00  0.00   A2
ATOM   567   CA   HIS  80   51.060 69.788 -10.360 1.00 43.79   A2
ATOM   568   CB   HIS  80   52.456 70.221 -10.810 1.00 43.58   A2
ATOM   569   CG   HIS  80   53.030 71.031  -9.690 1.00 43.75   A2
ATOM   570   CD2  HIS  80   53.484 70.497  -8.517 1.00 47.48   A2
ATOM   571   ND1  HIS  80   53.083 72.343  -9.567 1.00 44.24   A2
ATOM   572   HD1  HIS  80   52.842 73.004 -10.255 1.00  0.00   A2
ATOM   573   CE1  HIS  80   53.530 72.641  -8.376 1.00 44.47   A2
ATOM   574   NE2  HIS  80   53.772 71.520  -7.748 1.00 48.16   A2
```

FIG.5I

```
ATOM 575 HE2 HIS 80 54.103 71.444 -6.824 1.00 0.00 A2
ATOM 576 C HIS 80 50.094 70.978 -10.229 1.00 44.40 A2
ATOM 577 O HIS 80 49.643 71.294 -9.131 1.00 44.28 A2
ATOM 578 N SER 81 49.733 71.670 -11.309 1.00 45.13 A2
ATOM 579 H SER 81 50.136 71.459 -12.176 1.00 0.00 A2
ATOM 580 CA SER 81 48.738 72.742 -11.296 1.00 45.41 A2
ATOM 581 CB SER 81 48.612 73.347 -12.682 1.00 45.59 A2
ATOM 582 OG SER 81 49.894 73.444 -13.292 1.00 49.27 A2
ATOM 583 HG SER 81 50.058 72.670 -13.843 1.00 0.00 A2
ATOM 584 C SER 81 47.344 72.266 -10.856 1.00 44.85 A2
ATOM 585 O SER 81 46.604 73.064 -10.256 1.00 46.83 A2
ATOM 586 N GLY 82 46.946 71.010 -11.092 1.00 42.16 A2
ATOM 587 H GLY 82 47.513 70.411 -11.614 1.00 0.00 A2
ATOM 588 CA GLY 82 45.663 70.500 -10.650 1.00 39.39 A2
ATOM 589 C GLY 82 45.569 70.461 -9.139 1.00 39.30 A2
ATOM 590 O GLY 82 44.542 70.843 -8.544 1.00 39.64 A2
ATOM 591 N LEU 83 46.676 70.032 -8.521 1.00 37.57 A2
ATOM 592 H LEU 83 47.413 69.695 -9.075 1.00 0.00 A2
ATOM 593 CA LEU 83 46.826 70.007 -7.057 1.00 38.07 A2
ATOM 594 CB LEU 83 48.133 69.202 -6.748 1.00 35.67 A2
ATOM 595 CG LEU 83 48.071 67.736 -7.225 1.00 32.51 A2
ATOM 596 CD1 LEU 83 49.442 67.145 -7.319 1.00 29.77 A2
ATOM 597 CD2 LEU 83 47.180 66.973 -6.288 1.00 28.71 A2
ATOM 598 C LEU 83 46.836 71.386 -6.354 1.00 38.48 A2
ATOM 599 O LEU 83 46.392 71.627 -5.219 1.00 38.05 A2
ATOM 600 N PHE 84 47.366 72.338 -7.108 1.00 40.34 A2
ATOM 601 H PHE 84 47.804 72.078 -7.944 1.00 0.00 A2
ATOM 602 CA PHE 84 47.414 73.703 -6.688 1.00 41.54 A2
ATOM 603 CB PHE 84 48.163 74.531 -7.693 1.00 46.88 A2
ATOM 604 CG PHE 84 48.715 75.777 -6.988 1.00 55.09 A2
ATOM 605 CD1 PHE 84 49.521 75.622 -5.849 1.00 55.31 A2
ATOM 606 CD2 PHE 84 48.396 77.002 -7.469 1.00 55.79 A2
ATOM 607 CE1 PHE 84 50.004 76.737 -5.195 1.00 57.60 A2
ATOM 608 CE2 PHE 84 48.892 78.156 -6.796 1.00 57.25 A2
ATOM 609 CZ PHE 84 49.688 78.002 -5.667 1.00 58.34 A2
ATOM 610 C PHE 84 45.994 74.191 -6.591 1.00 40.47 A2
ATOM 611 O PHE 84 45.609 74.749 -5.558 1.00 42.71 A2
ATOM 612 N LEU 85 45.190 73.953 -7.624 1.00 38.64 A2
ATOM 613 H LEU 85 45.555 73.527 -8.429 1.00 0.00 A2
ATOM 614 CA LEU 85 43.794 74.335 -7.584 1.00 38.81 A2
ATOM 615 CB LEU 85 43.101 73.886 -8.839 1.00 41.27 A2
ATOM 616 CG LEU 85 41.673 74.403 -9.017 1.00 46.45 A2
ATOM 617 CD1 LEU 85 41.702 75.784 -9.719 1.00 47.80 A2
ATOM 618 CD2 LEU 85 40.860 73.359 -9.787 1.00 48.25 A2
ATOM 619 C LEU 85 43.079 73.731 -6.386 1.00 38.20 A2
ATOM 620 O LEU 85 42.498 74.469 -5.582 1.00 38.36 A2
ATOM 621 N TYR 86 43.150 72.405 -6.198 1.00 37.92 A2
ATOM 622 H TYR 86 43.637 71.850 -6.845 1.00 0.00 A2
ATOM 623 CA TYR 86 42.501 71.801 -5.057 1.00 37.15 A2
ATOM 624 CB TYR 86 42.598 70.255 -5.102 1.00 36.73 A2
ATOM 625 CG TYR 86 41.561 69.685 -6.081 1.00 33.66 A2
ATOM 626 CD1 TYR 86 41.946 69.312 -7.374 1.00 30.03 A2
ATOM 627 CE1 TYR 86 40.991 68.885 -8.280 1.00 30.08 A2
ATOM 628 CD2 TYR 86 40.224 69.623 -5.666 1.00 32.61 A2
ATOM 629 CE2 TYR 86 39.263 69.203 -6.574 1.00 31.66 A2
ATOM 630 CZ TYR 86 39.656 68.838 -7.868 1.00 30.57 A2
ATOM 631 OH TYR 86 38.670 68.428 -8.751 1.00 28.18 A2
ATOM 632 HH TYR 86 39.107 67.994 -9.485 1.00 0.00 A2
ATOM 633 C TYR 86 43.054 72.318 -3.746 1.00 37.75 A2
ATOM 634 O TYR 86 42.173 72.469 -2.889 1.00 39.52 A2
ATOM 635 N GLN 87 44.347 72.655 -3.478 1.00 36.93 A2
ATOM 636 H GLN 87 45.044 72.463 -4.140 1.00 0.00 A2
ATOM 637 CA GLN 87 44.749 73.332 -2.205 1.00 36.40 A2
ATOM 638 CB GLN 87 46.210 73.668 -2.255 1.00 39.56 A2
ATOM 639 CG GLN 87 47.126 72.993 -1.237 1.00 46.99 A2
ATOM 640 CD GLN 87 48.641 73.062 -1.576 1.00 50.96 A2
ATOM 641 OE1 GLN 87 49.144 72.623 -2.627 1.00 52.15 A2
ATOM 642 NE2 GLN 87 49.446 73.608 -0.663 1.00 52.96 A2
ATOM 643 HE21 GLN 87 49.055 73.957 0.164 1.00 0.00 A2
ATOM 644 HE22 GLN 87 50.396 73.621 -0.888 1.00 0.00 A2
ATOM 645 C GLN 87 43.941 74.652 -2.013 1.00 34.36 A2
ATOM 646 O GLN 87 43.414 74.990 -0.935 1.00 31.55 A2
```

FIG.5J

					x	y	z	occ	B	
ATOM	647	N	GLY	88	43.740	75.335	-3.159	1.00	32.73	A2
ATOM	648	H	GLY	88	44.165	75.005	-3.981	1.00	0.00	A2
ATOM	649	CA	GLY	88	42.948	76.546	-3.232	1.00	30.81	A2
ATOM	650	C	GLY	88	41.540	76.275	-2.731	1.00	30.47	A2
ATOM	651	O	GLY	88	41.130	76.819	-1.703	1.00	30.27	A2
ATOM	652	N	LEU	89	40.802	75.387	-3.406	1.00	29.01	A2
ATOM	653	H	LEU	89	41.220	74.912	-4.154	1.00	0.00	A2
ATOM	654	CA	LEU	89	39.447	75.102	-3.009	1.00	27.60	A2
ATOM	655	CB	LEU	89	38.922	74.073	-3.935	1.00	28.13	A2
ATOM	656	CG	LEU	89	38.764	74.583	-5.340	1.00	29.51	A2
ATOM	657	CD1	LEU	89	38.363	73.530	-6.364	1.00	24.13	A2
ATOM	658	CD2	LEU	89	37.673	75.637	-5.220	1.00	32.87	A2
ATOM	659	C	LEU	89	39.352	74.629	-1.583	1.00	29.88	A2
ATOM	660	O	LEU	89	38.427	75.012	-0.860	1.00	30.81	A2
ATOM	661	N	LEU	90	40.317	73.839	-1.094	1.00	32.59	A2
ATOM	662	H	LEU	90	41.101	73.626	-1.643	1.00	0.00	A2
ATOM	663	CA	LEU	90	40.182	73.274	0.235	1.00	33.41	A2
ATOM	664	CB	LEU	90	41.207	72.234	0.503	1.00	36.15	A2
ATOM	665	CG	LEU	90	41.075	70.971	-0.343	1.00	38.76	A2
ATOM	666	CD1	LEU	90	42.431	70.267	-0.456	1.00	37.21	A2
ATOM	667	CD2	LEU	90	39.995	70.099	0.279	1.00	40.54	A2
ATOM	668	C	LEU	90	40.342	74.319	1.255	1.00	34.24	A2
ATOM	669	O	LEU	90	39.711	74.256	2.313	1.00	35.57	A2
ATOM	670	N	GLN	91	41.188	75.291	0.940	1.00	35.24	A2
ATOM	671	H	GLN	91	41.663	75.284	0.078	1.00	0.00	A2
ATOM	672	CA	GLN	91	41.397	76.373	1.883	1.00	37.60	A2
ATOM	673	CB	GLN	91	42.557	77.182	1.363	1.00	39.65	A2
ATOM	674	CG	GLN	91	43.155	78.237	2.284	1.00	44.32	A2
ATOM	675	CD	GLN	91	44.348	78.799	1.542	1.00	46.96	A2
ATOM	676	OE1	GLN	91	45.235	78.083	1.068	1.00	47.42	A2
ATOM	677	NE2	GLN	91	44.376	80.092	1.341	1.00	46.82	A2
ATOM	678	HE21	GLN	91	43.690	80.685	1.700	1.00	0.00	A2
ATOM	679	HE22	GLN	91	45.108	80.331	0.741	1.00	0.00	A2
ATOM	680	C	GLN	91	40.129	77.231	2.061	1.00	37.22	A2
ATOM	681	O	GLN	91	39.718	77.530	3.186	1.00	36.21	A2
ATOM	682	N	ALA	92	39.456	77.570	0.943	1.00	38.63	A2
ATOM	683	H	ALA	92	39.808	77.205	0.098	1.00	0.00	A2
ATOM	684	CA	ALA	92	38.243	78.402	0.880	1.00	38.10	A2
ATOM	685	CB	ALA	92	37.657	78.436	-0.511	1.00	36.76	A2
ATOM	686	C	ALA	92	37.139	77.905	1.770	1.00	38.95	A2
ATOM	687	O	ALA	92	36.294	78.687	2.194	1.00	42.45	A2
ATOM	688	N	LEU	93	37.151	76.618	2.123	1.00	38.34	A2
ATOM	689	H	LEU	93	37.855	76.040	1.759	1.00	0.00	A2
ATOM	690	CA	LEU	93	36.111	76.018	2.972	1.00	36.90	A2
ATOM	691	CB	LEU	93	36.088	74.463	2.794	1.00	35.34	A2
ATOM	692	CG	LEU	93	35.725	73.992	1.378	1.00	33.55	A2
ATOM	693	CD1	LEU	93	36.159	72.583	1.129	1.00	33.26	A2
ATOM	694	CD2	LEU	93	34.254	74.167	1.215	1.00	32.18	A2
ATOM	695	C	LEU	93	36.264	76.353	4.426	1.00	36.44	A2
ATOM	696	O	LEU	93	35.473	75.917	5.256	1.00	35.17	A2
ATOM	697	N	GLU	94	37.357	77.019	4.736	1.00	38.19	A2
ATOM	698	H	GLU	94	38.022	77.167	4.035	1.00	0.00	A2
ATOM	699	CA	GLU	94	37.627	77.573	6.038	1.00	42.71	A2
ATOM	700	CB	GLU	94	36.931	78.947	6.165	1.00	47.38	A2
ATOM	701	CG	GLU	94	37.418	80.011	5.131	1.00	56.10	A2
ATOM	702	CD	GLU	94	36.423	81.153	4.862	1.00	60.26	A2
ATOM	703	OE1	GLU	94	35.728	81.109	3.823	1.00	60.76	A2
ATOM	704	OE2	GLU	94	36.331	82.054	5.721	1.00	61.64	A2
ATOM	705	C	GLU	94	37.245	76.701	7.198	1.00	43.90	A2
ATOM	706	O	GLU	94	36.624	77.172	8.167	1.00	45.70	A2
ATOM	707	N	GLY	95	37.641	75.410	7.001	1.00	44.03	A2
ATOM	708	H	GLY	95	38.024	75.192	6.127	1.00	0.00	A2
ATOM	709	CA	GLY	95	37.519	74.310	7.981	1.00	42.49	A2
ATOM	710	C	GLY	95	36.162	73.612	8.061	1.00	42.24	A2
ATOM	711	O	GLY	95	36.028	72.596	8.739	1.00	40.02	A2
ATOM	712	N	ILE	96	35.160	74.123	7.328	1.00	42.82	A2
ATOM	713	H	ILE	96	35.357	74.944	6.841	1.00	0.00	A2
ATOM	714	CA	ILE	96	33.760	73.692	7.312	1.00	42.12	A2
ATOM	715	CB	ILE	96	33.665	72.233	6.800	1.00	36.33	A2
ATOM	716	CG2	ILE	96	32.248	71.768	6.789	1.00	34.79	A2
ATOM	717	CG1	ILE	96	34.091	72.157	5.374	1.00	35.35	A2
ATOM	718	CD	ILE	96	34.051	70.743	4.738	1.00	33.64	A2

FIG.5K

ATOM	719	C	ILE	96	33.106	73.863	8.709	1.00	44.74	A2
ATOM	720	O	ILE	96	32.220	74.716	8.841	1.00	44.59	A2
ATOM	721	N	SER	97	33.467	73.154	9.780	1.00	46.84	A2
ATOM	722	H	SER	97	34.243	72.553	9.706	1.00	0.00	A2
ATOM	723	CA	SER	97	32.900	73.359	11.105	1.00	48.91	A2
ATOM	724	CB	SER	97	31.804	72.343	11.347	1.00	49.60	A2
ATOM	725	OG	SER	97	32.211	71.120	11.954	1.00	52.85	A2
ATOM	726	HG	SER	97	31.406	70.573	11.942	1.00	0.00	A2
ATOM	727	C	SER	97	34.045	73.143	12.077	1.00	50.64	A2
ATOM	728	O	SER	97	35.035	72.538	11.678	1.00	52.78	A2
ATOM	729	N	PRO	98	34.063	73.474	13.348	1.00	52.12	A2
ATOM	730	CD	PRO	98	33.002	74.170	14.016	1.00	52.90	A2
ATOM	731	CA	PRO	98	35.195	73.200	14.257	1.00	54.94	A2
ATOM	732	CB	PRO	98	34.750	73.717	15.600	1.00	54.78	A2
ATOM	733	CG	PRO	98	33.772	74.777	15.182	1.00	55.48	A2
ATOM	734	C	PRO	98	35.591	71.723	14.336	1.00	56.75	A2
ATOM	735	O	PRO	98	36.738	71.274	14.468	1.00	57.85	A2
ATOM	736	N	GLU	99	34.509	70.971	14.214	1.00	58.21	A2
ATOM	737	H	GLU	99	33.652	71.400	14.028	1.00	0.00	A2
ATOM	738	CA	GLU	99	34.543	69.537	14.281	1.00	58.48	A2
ATOM	739	CB	GLU	99	33.111	69.104	14.304	1.00	63.30	A2
ATOM	740	CG	GLU	99	32.958	67.702	14.852	1.00	71.04	A2
ATOM	741	CD	GLU	99	32.076	66.838	13.962	1.00	76.95	A2
ATOM	742	OE1	GLU	99	32.209	65.608	14.079	1.00	80.63	A2
ATOM	743	OE2	GLU	99	31.295	67.382	13.153	1.00	77.99	A2
ATOM	744	C	GLU	99	35.298	69.025	13.074	1.00	55.31	A2
ATOM	745	O	GLU	99	36.251	68.270	13.210	1.00	55.96	A2
ATOM	746	N	LEU	100	34.916	69.475	11.891	1.00	51.23	A2
ATOM	747	H	LEU	100	34.214	70.159	11.841	1.00	0.00	A2
ATOM	748	CA	LEU	100	35.577	69.052	10.678	1.00	48.08	A2
ATOM	749	CB	LEU	100	34.627	69.341	9.574	1.00	45.52	A2
ATOM	750	CG	LEU	100	33.544	68.337	9.674	1.00	45.39	A2
ATOM	751	CD1	LEU	100	32.207	68.972	9.458	1.00	46.40	A2
ATOM	752	CD2	LEU	100	33.851	67.245	8.677	1.00	47.48	A2
ATOM	753	C	LEU	100	36.956	69.629	10.368	1.00	46.77	A2
ATOM	754	O	LEU	100	37.578	69.244	9.357	1.00	46.62	A2
ATOM	755	N	GLY	101	37.441	70.505	11.272	1.00	45.40	A2
ATOM	756	H	GLY	101	36.893	70.704	12.056	1.00	0.00	A2
ATOM	757	CA	GLY	101	38.703	71.238	11.126	1.00	42.52	A2
ATOM	758	C	GLY	101	39.885	70.334	10.798	1.00	40.73	A2
ATOM	759	O	GLY	101	40.475	70.402	9.710	1.00	40.69	A2
ATOM	760	N	PRO	102	40.250	69.441	11.708	1.00	38.61	A2
ATOM	761	CD	PRO	102	39.676	69.350	13.027	1.00	39.26	A2
ATOM	762	CA	PRO	102	41.390	68.566	11.606	1.00	37.30	A2
ATOM	763	CB	PRO	102	41.294	67.690	12.775	1.00	39.36	A2
ATOM	764	CG	PRO	102	40.799	68.687	13.776	1.00	41.02	A2
ATOM	765	C	PRO	102	41.364	67.795	10.331	1.00	37.15	A2
ATOM	766	O	PRO	102	42.358	67.854	9.600	1.00	38.88	A2
ATOM	767	N	THR	103	40.223	67.167	10.045	1.00	35.36	A2
ATOM	768	H	THR	103	39.466	67.223	10.662	1.00	0.00	A2
ATOM	769	CA	THR	103	40.051	66.386	8.843	1.00	34.62	A2
ATOM	770	CB	THR	103	38.592	65.888	8.715	1.00	34.07	A2
ATOM	771	OG1	THR	103	38.356	65.240	9.936	1.00	35.43	A2
ATOM	772	HG1	THR	103	38.011	65.896	10.548	1.00	0.00	A2
ATOM	773	CG2	THR	103	38.312	64.896	7.594	1.00	31.29	A2
ATOM	774	C	THR	103	40.417	67.215	7.625	1.00	34.61	A2
ATOM	775	O	THR	103	41.091	66.665	6.738	1.00	38.16	A2
ATOM	776	N	LEU	104	40.054	68.498	7.529	1.00	32.49	A2
ATOM	777	H	LEU	104	39.504	68.923	8.229	1.00	0.00	A2
ATOM	778	CA	LEU	104	40.471	69.267	6.370	1.00	30.49	A2
ATOM	779	CB	LEU	104	39.616	70.430	6.242	1.00	33.51	A2
ATOM	780	CG	LEU	104	38.356	69.996	5.611	1.00	36.61	A2
ATOM	781	CD1	LEU	104	37.222	70.621	6.381	1.00	39.43	A2
ATOM	782	CD2	LEU	104	38.418	70.294	4.132	1.00	37.89	A2
ATOM	783	C	LEU	104	41.904	69.727	6.414	1.00	28.48	A2
ATOM	784	O	LEU	104	42.583	69.825	5.398	1.00	28.47	A2
ATOM	785	N	ASP	105	42.449	69.949	7.574	1.00	26.99	A2
ATOM	786	H	ASP	105	41.903	69.912	8.388	1.00	0.00	A2
ATOM	787	CA	ASP	105	43.822	70.307	7.613	1.00	28.67	A2
ATOM	788	CB	ASP	105	44.139	70.584	9.038	1.00	33.06	A2
ATOM	789	CG	ASP	105	43.438	71.808	9.593	1.00	35.46	A2
ATOM	790	OD1	ASP	105	43.085	72.726	8.836	1.00	38.42	A2

FIG.5L

ATOM	791	OD2	ASP	105	43.244	71.816	10.808	1.00	39.10	A2
ATOM	792	C	ASP	105	44.701	69.206	7.032	1.00	28.90	A2
ATOM	793	O	ASP	105	45.551	69.479	6.175	1.00	29.62	A2
ATOM	794	N	THR	106	44.415	67.950	7.401	1.00	26.86	A2
ATOM	795	H	THR	106	43.674	67.826	8.029	1.00	0.00	A2
ATOM	796	CA	THR	106	45.143	66.770	6.935	1.00	24.81	A2
ATOM	797	CB	THR	106	44.558	65.456	7.477	1.00	26.03	A2
ATOM	798	OG1	THR	106	44.680	65.566	8.894	1.00	31.53	A2
ATOM	799	HG1	THR	106	44.069	66.223	9.242	1.00	0.00	A2
ATOM	800	CG2	THR	106	45.258	64.220	7.011	1.00	20.90	A2
ATOM	801	C	THR	106	45.073	66.684	5.460	1.00	23.75	A2
ATOM	802	O	THR	106	46.065	66.411	4.812	1.00	24.68	A2
ATOM	803	N	LEU	107	43.887	66.917	4.946	1.00	24.30	A2
ATOM	804	H	LEU	107	43.145	67.176	5.528	1.00	0.00	A2
ATOM	805	CA	LEU	107	43.668	66.783	3.531	1.00	27.29	A2
ATOM	806	CB	LEU	107	42.158	66.913	3.273	1.00	25.45	A2
ATOM	807	CG	LEU	107	41.642	66.888	1.863	1.00	26.24	A2
ATOM	808	CD1	LEU	107	42.095	65.649	1.158	1.00	26.41	A2
ATOM	809	CD2	LEU	107	40.140	66.925	1.914	1.00	27.62	A2
ATOM	810	C	LEU	107	44.485	67.848	2.819	1.00	28.01	A2
ATOM	811	O	LEU	107	45.154	67.555	1.823	1.00	30.72	A2
ATOM	812	N	GLN	108	44.540	69.055	3.373	1.00	28.52	A2
ATOM	813	H	GLN	108	44.030	69.221	4.194	1.00	0.00	A2
ATOM	814	CA	GLN	108	45.343	70.132	2.792	1.00	28.38	A2
ATOM	815	CB	GLN	108	45.138	71.363	3.630	1.00	30.15	A2
ATOM	816	CG	GLN	108	43.711	71.787	3.542	1.00	32.67	A2
ATOM	817	CD	GLN	108	43.606	73.192	4.048	1.00	35.24	A2
ATOM	818	OE1	GLN	108	43.085	73.484	5.125	1.00	36.07	A2
ATOM	819	NE2	GLN	108	44.189	74.044	3.213	1.00	33.58	A2
ATOM	820	HE21	GLN	108	44.582	73.701	2.386	1.00	0.00	A2
ATOM	821	HE22	GLN	108	44.195	74.986	3.471	1.00	0.00	A2
ATOM	822	C	GLN	108	46.840	69.842	2.675	1.00	26.40	A2
ATOM	823	O	GLN	108	47.450	69.955	1.597	1.00	27.57	A2
ATOM	824	N	LEU	109	47.388	69.473	3.833	1.00	25.81	A2
ATOM	825	H	LEU	109	46.795	69.495	4.615	1.00	0.00	A2
ATOM	826	CA	LEU	109	48.764	69.003	4.043	1.00	27.96	A2
ATOM	827	CB	LEU	109	48.951	68.637	5.513	1.00	29.41	A2
ATOM	828	CG	LEU	109	48.712	69.771	6.520	1.00	31.78	A2
ATOM	829	CD1	LEU	109	48.750	69.188	7.933	1.00	29.16	A2
ATOM	830	CD2	LEU	109	49.724	70.889	6.285	1.00	32.19	A2
ATOM	831	C	LEU	109	49.168	67.790	3.186	1.00	26.80	A2
ATOM	832	O	LEU	109	50.214	67.721	2.544	1.00	26.81	A2
ATOM	833	N	ASP	110	48.305	66.807	3.090	1.00	25.98	A2
ATOM	834	H	ASP	110	47.471	66.835	3.600	1.00	0.00	A2
ATOM	835	CA	ASP	110	48.590	65.684	2.250	1.00	23.32	A2
ATOM	836	CB	ASP	110	47.577	64.570	2.553	1.00	26.34	A2
ATOM	837	CG	ASP	110	47.905	63.878	3.894	1.00	31.10	A2
ATOM	838	OD1	ASP	110	47.070	63.093	4.323	1.00	34.98	A2
ATOM	839	OD2	ASP	110	48.958	64.107	4.535	1.00	34.06	A2
ATOM	840	C	ASP	110	48.557	66.138	0.842	1.00	21.31	A2
ATOM	841	O	ASP	110	49.493	65.711	0.165	1.00	20.63	A2
ATOM	842	N	VAL	111	47.627	66.998	0.363	1.00	20.80	A2
ATOM	843	H	VAL	111	46.900	67.310	0.944	1.00	0.00	A2
ATOM	844	CA	VAL	111	47.711	67.454	-1.019	1.00	20.44	A2
ATOM	845	CB	VAL	111	46.531	68.364	-1.376	1.00	23.60	A2
ATOM	846	CG1	VAL	111	46.615	68.946	-2.808	1.00	23.04	A2
ATOM	847	CG2	VAL	111	45.289	67.497	-1.371	1.00	24.30	A2
ATOM	848	C	VAL	111	49.006	68.224	-1.245	1.00	20.82	A2
ATOM	849	O	VAL	111	49.617	68.006	-2.303	1.00	19.22	A2
ATOM	850	N	ALA	112	49.442	69.063	-0.267	1.00	21.84	A2
ATOM	851	H	ALA	112	48.839	69.190	0.492	1.00	0.00	A2
ATOM	852	CA	ALA	112	50.708	69.805	-0.295	1.00	24.16	A2
ATOM	853	CB	ALA	112	50.861	70.561	1.011	1.00	22.69	A2
ATOM	854	C	ALA	112	51.931	68.878	-0.486	1.00	28.58	A2
ATOM	855	O	ALA	112	52.778	69.026	-1.390	1.00	32.53	A2
ATOM	856	N	ASP	113	52.086	67.852	0.343	1.00	30.21	A2
ATOM	857	H	ASP	113	51.507	67.817	1.130	1.00	0.00	A2
ATOM	858	CA	ASP	113	53.084	66.846	0.166	1.00	31.70	A2
ATOM	859	CB	ASP	113	52.706	65.659	0.953	1.00	36.31	A2
ATOM	860	CG	ASP	113	53.170	65.758	2.357	1.00	42.27	A2
ATOM	861	OD1	ASP	113	52.559	65.109	3.203	1.00	46.37	A2
ATOM	862	OD2	ASP	113	54.160	66.461	2.589	1.00	48.93	A2

FIG.5M

```
ATOM  863 C   ASP 113  53.315 66.361 -1.239 1.00 32.82 A2
ATOM  864 O   ASP 113  54.433 66.308 -1.754 1.00 36.25 A2
ATOM  865 N   PHE 114  52.187 65.978 -1.830 1.00 30.94 A2
ATOM  866 H   PHE 114  51.344 66.164 -1.361 1.00  0.00 A2
ATOM  867 CA  PHE 114  52.109 65.328 -3.103 1.00 27.84 A2
ATOM  868 CB  PHE 114  50.708 64.794 -3.226 1.00 23.18 A2
ATOM  869 CG  PHE 114  50.565 63.928 -4.420 1.00 21.04 A2
ATOM  870 CD1 PHE 114  51.623 63.225 -4.938 1.00 24.05 A2
ATOM  871 CD2 PHE 114  49.369 63.914 -5.046 1.00 22.37 A2
ATOM  872 CE1 PHE 114  51.476 62.514 -6.102 1.00 24.54 A2
ATOM  873 CE2 PHE 114  49.211 63.207 -6.212 1.00 21.33 A2
ATOM  874 CZ  PHE 114  50.263 62.509 -6.741 1.00 24.71 A2
ATOM  875 C   PHE 114  52.453 66.291 -4.190 1.00 29.20 A2
ATOM  876 O   PHE 114  53.072 65.883 -5.158 1.00 30.84 A2
ATOM  877 N   ALA 115  52.057 67.554 -4.058 1.00 31.99 A2
ATOM  878 H   ALA 115  51.446 67.768 -3.317 1.00  0.00 A2
ATOM  879 CA  ALA 115  52.423 68.655 -4.952 1.00 31.29 A2
ATOM  880 CB  ALA 115  51.824 69.939 -4.420 1.00 30.65 A2
ATOM  881 C   ALA 115  53.936 68.787 -4.976 1.00 31.31 A2
ATOM  882 O   ALA 115  54.539 68.823 -6.044 1.00 30.36 A2
ATOM  883 N   THR 116  54.551 68.846 -3.813 1.00 32.20 A2
ATOM  884 H   THR 116  54.013 68.910 -2.992 1.00  0.00 A2
ATOM  885 CA  THR 116  55.998 68.897 -3.656 1.00 34.91 A2
ATOM  886 CB  THR 116  56.325 68.953 -2.150 1.00 35.78 A2
ATOM  887 OG1 THR 116  55.564 70.038 -1.576 1.00 35.58 A2
ATOM  888 HG1 THR 116  54.942 69.644 -0.939 1.00  0.00 A2
ATOM  889 CG2 THR 116  57.816 69.050 -1.921 1.00 35.38 A2
ATOM  890 C   THR 116  56.714 67.726 -4.304 1.00 37.14 A2
ATOM  891 O   THR 116  57.641 67.937 -5.066 1.00 39.27 A2
ATOM  892 N   THR 117  56.318 66.485 -4.045 1.00 39.05 A2
ATOM  893 H   THR 117  55.615 66.383 -3.369 1.00  0.00 A2
ATOM  894 CA  THR 117  56.840 65.269 -4.630 1.00 40.23 A2
ATOM  895 CB  THR 117  55.909 64.090 -4.216 1.00 39.99 A2
ATOM  896 OG1 THR 117  56.149 63.920 -2.820 1.00 41.66 A2
ATOM  897 HG1 THR 117  55.653 64.559 -2.286 1.00  0.00 A2
ATOM  898 CG2 THR 117  56.110 62.781 -4.981 1.00 38.23 A2
ATOM  899 C   THR 117  56.882 65.417 -6.134 1.00 43.42 A2
ATOM  900 O   THR 117  57.934 65.253 -6.749 1.00 46.29 A2
ATOM  901 N   ILE 118  55.763 65.777 -6.741 1.00 45.87 A2
ATOM  902 H   ILE 118  54.962 65.942 -6.200 1.00  0.00 A2
ATOM  903 CA  ILE 118  55.659 65.914 -8.182 1.00 47.97 A2
ATOM  904 CB  ILE 118  54.170 66.271 -8.452 1.00 47.69 A2
ATOM  905 CG2 ILE 118  54.041 66.930 -9.835 1.00 47.03 A2
ATOM  906 CG1 ILE 118  53.302 65.011 -8.244 1.00 44.00 A2
ATOM  907 CD  ILE 118  53.651 63.883 -9.236 1.00 43.71 A2
ATOM  908 C   ILE 118  56.647 66.932 -8.724 1.00 50.69 A2
ATOM  909 O   ILE 118  57.390 66.676 -9.681 1.00 49.98 A2
ATOM  910 N   TRP 119  56.697 68.061 -8.015 1.00 54.68 A2
ATOM  911 H   TRP 119  56.164 68.135 -7.197 1.00  0.00 A2
ATOM  912 CA  TRP 119  57.575 69.142 -8.399 1.00 58.98 A2
ATOM  913 CB  TRP 119  57.392 70.367 -7.477 1.00 59.84 A2
ATOM  914 CG  TRP 119  58.051 71.529 -8.196 1.00 62.64 A2
ATOM  915 CD2 TRP 119  57.596 72.211 -9.307 1.00 63.78 A2
ATOM  916 CE2 TRP 119  58.699 72.955 -9.643 1.00 62.55 A2
ATOM  917 CE3 TRP 119  56.465 72.314 -10.080 1.00 66.02 A2
ATOM  918 CD1 TRP 119  59.322 71.870 -7.863 1.00 64.12 A2
ATOM  919 NE1 TRP 119  59.680 72.727 -8.784 1.00 65.00 A2
ATOM  920 HE1 TRP 119  60.568 73.140 -8.828 1.00  0.00 A2
ATOM  921 CZ2 TRP 119  58.726 73.794 -10.714 1.00 62.90 A2
ATOM  922 CZ3 TRP 119  56.469 73.157 -11.170 1.00 65.18 A2
ATOM  923 CH2 TRP 119  57.591 73.887 -11.481 1.00 64.40 A2
ATOM  924 C   TRP 119  59.021 68.664 -8.352 1.00 61.26 A2
ATOM  925 O   TRP 119  59.748 68.788 -9.343 1.00 62.12 A2
ATOM  926 N   GLN 120  59.447 68.065 -7.249 1.00 62.91 A2
ATOM  927 H   GLN 120  58.811 67.961 -6.519 1.00  0.00 A2
ATOM  928 CA  GLN 120  60.786 67.504 -7.113 1.00 65.16 A2
ATOM  929 CB  GLN 120  60.900 66.800 -5.780 1.00 66.56 A2
ATOM  930 CG  GLN 120  60.627 67.678 -4.582 1.00 67.18 A2
ATOM  931 CD  GLN 120  60.725 66.907 -3.284 1.00 67.77 A2
ATOM  932 OE1 GLN 120  61.221 67.465 -2.319 1.00 69.31 A2
ATOM  933 NE2 GLN 120  60.305 65.654 -3.129 1.00 67.39 A2
ATOM  934 HE21 GLN 120 59.903 65.174 -3.877 1.00  0.00 A2
```

FIG. 5N

```
ATOM  935 HE22 GLN 120   60.441 65.282  -2.234 1.00 0.00  A2
ATOM  936 C   GLN 120   61.169 66.509  -8.222 1.00 66.22 A2
ATOM  937 O   GLN 120   62.326 66.421  -8.662 1.00 66.50 A2
ATOM  938 N   GLN 121   60.202 65.745  -8.706 1.00 67.10 A2
ATOM  939 H   GLN 121   59.307 65.754  -8.303 1.00 0.00  A2
ATOM  940 CA  GLN 121   60.480 64.878  -9.812 1.00 68.66 A2
ATOM  941 CB  GLN 121   59.292 63.971 -10.070 1.00 67.96 A2
ATOM  942 CG  GLN 121   59.614 62.937 -11.128 1.00 68.89 A2
ATOM  943 CD  GLN 121   60.940 62.236 -10.852 1.00 71.37 A2
ATOM  944 OE1 GLN 121   61.212 61.706  -9.777 1.00 71.70 A2
ATOM  945 NE2 GLN 121   61.879 62.262 -11.786 1.00 74.41 A2
ATOM  946 HE21 GLN 121  61.707 62.729 -12.627 1.00 0.00  A2
ATOM  947 HE22 GLN 121  62.736 61.859 -11.541 1.00 0.00  A2
ATOM  948 C   GLN 121   60.760 65.743 -11.045 1.00 70.48 A2
ATOM  949 O   GLN 121   61.671 65.436 -11.827 1.00 70.94 A2
ATOM  950 N   MET 122   60.019 66.846 -11.236 1.00 71.67 A2
ATOM  951 H   MET 122   59.351 67.087 -10.555 1.00 0.00  A2
ATOM  952 CA  MET 122   60.190 67.688 -12.412 1.00 72.62 A2
ATOM  953 CB  MET 122   59.173 68.819 -12.448 1.00 73.12 A2
ATOM  954 CC  MET 122   57.880 68.343 -13.083 1.00 73.64 A2
ATOM  955 SD  MET 122   56.669 69.662 -13.295 1.00 75.44 A2
ATOM  956 CE  MET 122   55.695 69.349 -11.861 1.00 76.43 A2
ATOM  957 C   MET 122   61.566 68.281 -12.411 1.00 73.22 A2
ATOM  958 O   MET 122   62.240 68.287 -13.441 1.00 73.03 A2
ATOM  959 N   GLU 123   61.991 68.697 -11.223 1.00 74.74 A2
ATOM  960 H   GLU 123   61.372 68.617 -10.466 1.00 0.00  A2
ATOM  961 CA  GLU 123   63.305 69.262 -11.018 1.00 75.95 A2
ATOM  962 CB  GLU 123   63.484 69.665  -9.597 1.00 75.72 A2
ATOM  963 CG  GLU 123   62.644 70.906  -9.500 1.00 79.11 A2
ATOM  964 CD  GLU 123   62.651 71.529  -8.122 1.00 83.02 A2
ATOM  965 OE1 GLU 123   62.741 72.763  -8.057 1.00 84.15 A2
ATOM  966 OE2 GLU 123   62.543 70.789  -7.133 1.00 84.45 A2
ATOM  967 C   GLU 123   64.381 68.280 -11.386 1.00 77.17 A2
ATOM  968 O   GLU 123   65.092 68.558 -12.356 1.00 78.22 A2
ATOM  969 N   GLU 124   64.504 67.110 -10.765 1.00 77.66 A2
ATOM  970 H   GLU 124   63.867 66.852 -10.060 1.00 0.00  A2

ATOM  971 CA  GLU 124   65.574 66.215 -11.167 1.00 78.47 A2
ATOM  972 CB  GLU 124   65.600 65.051 -10.195 1.00 80.79 A2
ATOM  973 CG  GLU 124   64.387 64.132 -10.150 1.00 83.29 A2
ATOM  974 CD  GLU 124   64.375 63.248  -8.908 1.00 85.51 A2
ATOM  975 OE1 GLU 124   64.733 63.729  -7.824 1.00 86.84 A2
ATOM  976 OE2 GLU 124   64.006 62.075  -9.024 1.00 86.39 A2
ATOM  977 C   GLU 124   65.534 65.705 -12.612 1.00 78.01 A2
ATOM  978 O   GLU 124   66.480 65.057 -13.060 1.00 78.91 A2
ATOM  979 N   LEU 125   64.460 65.943 -13.363 1.00 77.11 A2
ATOM  980 H   LEU 125   63.666 66.340 -12.945 1.00 0.00  A2
ATOM  981 CA  LEU 125   64.387 65.583 -14.771 1.00 76.23 A2
ATOM  982 CB  LEU 125   63.061 64.832 -14.952 1.00 76.88 A2
ATOM  983 CG  LEU 125   62.392 64.382 -16.263 1.00 76.63 A2
ATOM  984 CD1 LEU 125   63.350 63.754 -17.226 1.00 75.84 A2
ATOM  985 CD2 LEU 125   61.309 63.402 -15.839 1.00 75.89 A2
ATOM  986 C   LEU 125   64.506 66.827 -15.648 1.00 75.84 A2
ATOM  987 O   LEU 125   64.360 66.788 -16.871 1.00 75.36 A2
ATOM  988 N   GLY 126   64.759 67.968 -15.027 1.00 75.90 A2
ATOM  989 H   GLY 126   64.741 67.976 -14.056 1.00 0.00  A2
ATOM  990 CA  GLY 126   64.968 69.213 -15.736 1.00 77.58 A2
ATOM  991 C   GLY 126   63.697 69.814 -16.330 1.00 78.63 A2
ATOM  992 O   GLY 126   63.735 70.736 -17.146 1.00 78.55 A2
ATOM  993 N   MET 127   62.524 69.343 -15.933 1.00 80.08 A2
ATOM  994 H   MET 127   62.522 68.603 -15.293 1.00 0.00  A2
ATOM  995 CA  MET 127   61.266 69.902 -16.415 1.00 81.46 A2
ATOM  996 CB  MET 127   60.191 68.802 -16.361 1.00 81.86 A2
ATOM  997 CG  MET 127   60.708 67.599 -17.147 1.00 82.66 A2
ATOM  998 SD  MET 127   59.682 66.115 -17.282 1.00 83.70 A2
ATOM  999 CE  MET 127   60.236 65.620 -18.900 1.00 83.23 A2
ATOM 1000 C   MET 127   60.847 71.131 -15.599 1.00 82.18 A2
ATOM 1001 OT1 MET 127   60.116 71.958 -16.142 1.00 83.86 A2
ATOM 1002 OT2 MET 127   61.267 71.285 -14.446 1.00 82.04 A2
ATOM 1003 CB  MET 138   39.323 80.595  -4.492 1.00 59.39 A3
ATOM 1004 CG  MET 138   40.123 79.298  -4.421 1.00 57.97 A3
ATOM 1005 SD  MET 138   40.561 78.973  -6.145 1.00 60.85 A3
ATOM 1006 CE  MET 138   41.129 77.310  -6.351 1.00 61.48 A3
```

FIG.50

```
ATOM 1007 C   MET 138 37.021 81.072 -5.454 1.00 60.26 A3
ATOM 1008 O   MET 138 36.832 82.262 -5.181 1.00 62.98 A3
ATOM 1009 HT1 MET 138 38.497 82.600 -6.075 1.00 0.00 A3
ATOM 1010 HT2 MET 138 38.313 81.757 -7.529 1.00 0.00 A3
ATOM 1011 N   MET 138 38.839 81.784 -6.639 1.00 60.49 A3
ATOM 1012 HT3 MET 138 39.865 81.816 -6.768 1.00 0.00 A3
ATOM 1013 CA  MET 138 38.445 80.672 -5.787 1.00 60.51 A3
ATOM 1014 N   PRO 139 35.995 80.242 -5.612 1.00 57.82 A3
ATOM 1015 CD  PRO 139 36.028 79.060 -6.448 1.00 58.10 A3
ATOM 1016 CA  PRO 139 34.654 80.538 -5.142 1.00 54.67 A3
ATOM 1017 CB  PRO 139 33.870 79.323 -5.525 1.00 54.54 A3
ATOM 1018 CG  PRO 139 34.945 78.290 -5.755 1.00 58.20 A3
ATOM 1019 C   PRO 139 34.588 80.875 -3.664 1.00 52.24 A3
ATOM 1020 O   PRO 139 35.507 80.623 -2.882 1.00 51.89 A3
ATOM 1021 N   ALA 140 33.499 81.547 -3.342 1.00 49.86 A3
ATOM 1022 H   ALA 140 32.789 81.676 -4.005 1.00 0.00 A3
ATOM 1023 CA  ALA 140 33.234 81.926 -1.994 1.00 49.39 A3
ATOM 1024 CB  ALA 140 32.966 83.413 -1.895 1.00 49.94 A3
ATOM 1025 C   ALA 140 31.978 81.153 -1.590 1.00 49.25 A3
ATOM 1026 O   ALA 140 30.889 81.162 -2.205 1.00 49.06 A3
ATOM 1027 N   PHE 141 32.293 80.442 -0.506 1.00 47.48 A3
ATOM 1028 H   PHE 141 33.190 80.550 -0.122 1.00 0.00 A3
ATOM 1029 CA  PHE 141 31.401 79.552 0.208 1.00 45.66 A3
ATOM 1030 CB  PHE 141 32.215 78.305 0.792 1.00 40.28 A3
ATOM 1031 CG  PHE 141 32.684 77.404 -0.349 1.00 35.35 A3
ATOM 1032 CD1 PHE 141 31.800 76.591 -1.006 1.00 34.39 A3
ATOM 1033 CD2 PHE 141 33.966 77.497 -0.830 1.00 37.69 A3
ATOM 1034 CE1 PHE 141 32.174 75.895 -2.133 1.00 34.00 A3
ATOM 1035 CE2 PHE 141 34.358 76.807 -1.956 1.00 36.69 A3
ATOM 1036 CZ  PHE 141 33.449 76.001 -2.614 1.00 37.29 A3
ATOM 1037 C   PHE 141 31.003 80.580 1.242 1.00 46.54 A3
ATOM 1038 O   PHE 141 31.584 80.664 2.317 1.00 48.26 A3
ATOM 1039 N   ALA 142 30.067 81.452 0.843 1.00 47.38 A3
ATOM 1040 H   ALA 142 29.624 81.295 -0.020 1.00 0.00 A3
ATOM 1041 CA  ALA 142 29.581 82.564 1.668 1.00 46.06 A3
ATOM 1042 CB  ALA 142 28.731 83.546 0.879 1.00 45.04 A3
ATOM 1043 C   ALA 142 28.703 82.132 2.802 1.00 45.27 A3
ATOM 1044 O   ALA 142 28.343 83.002 3.584 1.00 47.38 A3
ATOM 1045 N   SER 143 28.318 80.860 2.899 1.00 43.36 A3
ATOM 1046 H   SER 143 28.724 80.201 2.303 1.00 0.00 A3
ATOM 1047 CA  SER 143 27.377 80.392 3.897 1.00 41.94 A3
ATOM 1048 CB  SER 143 26.036 80.129 3.181 1.00 44.17 A3
ATOM 1049 OG  SER 143 25.323 78.918 3.536 1.00 48.18 A3
ATOM 1050 HG  SER 143 24.455 78.974 3.098 1.00 0.00 A3
ATOM 1051 C   SER 143 27.877 79.145 4.602 1.00 39.79 A3
ATOM 1052 O   SER 143 28.763 78.452 4.132 1.00 38.50 A3
ATOM 1053 N   ALA 144 27.218 78.775 5.683 1.00 39.10 A3
ATOM 1054 H   ALA 144 26.449 79.312 5.960 1.00 0.00 A3
ATOM 1055 CA  ALA 144 27.566 77.586 6.411 1.00 39.22 A3
ATOM 1056 CB  ALA 144 26.982 77.598 7.802 1.00 36.97 A3
ATOM 1057 C   ALA 144 26.964 76.420 5.627 1.00 41.58 A3
ATOM 1058 O   ALA 144 27.706 75.448 5.444 1.00 42.07 A3
ATOM 1059 N   PHE 145 25.719 76.407 5.076 1.00 40.77 A3
ATOM 1060 H   PHE 145 25.149 77.203 5.110 1.00 0.00 A3
ATOM 1061 CA  PHE 145 25.307 75.234 4.312 1.00 39.31 A3
ATOM 1062 CB  PHE 145 23.877 75.396 3.798 1.00 36.46 A3
ATOM 1063 CG  PHE 145 23.477 74.452 2.641 1.00 31.91 A3
ATOM 1064 CD1 PHE 145 23.579 74.900 1.323 1.00 29.02 A3
ATOM 1065 CD2 PHE 145 23.013 73.185 2.916 1.00 29.40 A3
ATOM 1066 CE1 PHE 145 23.225 74.100 0.277 1.00 28.34 A3
ATOM 1067 CE2 PHE 145 22.661 72.389 1.858 1.00 28.80 A3
ATOM 1068 CZ  PHE 145 22.764 72.831 0.549 1.00 30.58 A3
ATOM 1069 C   PHE 145 26.266 75.071 3.120 1.00 40.44 A3
ATOM 1070 O   PHE 145 26.556 73.938 2.697 1.00 40.55 A3
ATOM 1071 N   GLN 146 26.745 76.232 2.619 1.00 39.11 A3
ATOM 1072 H   GLN 146 26.437 77.073 3.015 1.00 0.00 A3
ATOM 1073 CA  GLN 146 27.660 76.263 1.511 1.00 38.01 A3
ATOM 1074 CB  GLN 146 27.907 77.644 1.054 1.00 38.92 A3
ATOM 1075 CG  GLN 146 26.884 78.066 0.049 1.00 43.26 A3
ATOM 1076 CD  GLN 146 27.171 79.440 -0.522 1.00 45.37 A3
ATOM 1077 OE1 GLN 146 27.851 80.253 0.083 1.00 47.57 A3
ATOM 1078 NE2 GLN 146 26.689 79.793 -1.692 1.00 47.50 A3
```

```
ATOM 1079 HE21 GLN 146 26.149 79.149 -2.190 1.00  0.00
ATOM 1080 HE22 GLN 146 26.913 80.690 -2.021 1.00  0.00
ATOM 1081 C    GLN 146 29.005 75.670  1.836 1.00 37.25 A3
ATOM 1082 O    GLN 146 29.634 75.093  0.950 1.00 38.28 A3
ATOM 1083 N    ARG 147 29.511 75.775  3.054 1.00 36.37 A3
ATOM 1084 H    ARG 147 29.044 76.300  3.738 1.00  0.00 A3
ATOM 1085 CA   ARG 147 30.798 75.180  3.357 1.00 35.68 A3
ATOM 1086 CB   ARG 147 31.299 75.574  4.713 1.00 37.12 A3
ATOM 1087 CG   ARG 147 31.730 77.016  4.697 1.00 42.68 A3
ATOM 1088 CD   ARG 147 32.034 77.494  6.093 1.00 49.54 A3
ATOM 1089 NE   ARG 147 32.674 78.774  5.877 1.00 58.21 A3
ATOM 1090 HE   ARG 147 32.475 79.252  5.045 1.00  0.00 A3
ATOM 1091 CZ   ARG 147 33.519 79.373  6.742 1.00 62.77 A3
ATOM 1092 NH1  ARG 147 33.905 78.868  7.936 1.00 63.96 A3
ATOM 1093 HH11 ARG 147 34.545 79.379  8.510 1.00  0.00 A3
ATOM 1094 HH12 ARG 147 33.561 77.980  8.239 1.00  0.00 A3
ATOM 1095 NH2  ARG 147 33.960 80.584  6.403 1.00 64.80 A3
ATOM 1096 HH21 ARG 147 34.599 81.069  6.999 1.00  0.00 A3
ATOM 1097 HH22 ARG 147 33.665 80.996  5.541 1.00  0.00 A3
ATOM 1098 C    ARG 147 30.570 73.702  3.337 1.00 34.91 A3
ATOM 1099 O    ARG 147 31.233 73.050  2.539 1.00 34.56 A3
ATOM 1100 N    ALA 148 29.544 73.194  4.040 1.00 33.44 A3
ATOM 1101 H    ALA 148 28.926 73.818  4.482 1.00  0.00 A3
ATOM 1102 CA   ALA 148 29.358 71.754  4.172 1.00 33.92 A3
ATOM 1103 CB   ALA 148 28.217 71.426  5.163 1.00 32.85 A3
ATOM 1104 C    ALA 148 29.077 71.095  2.843 1.00 33.40 A3
ATOM 1105 O    ALA 148 29.765 70.141  2.457 1.00 34.31 A3
ATOM 1106 N    ALA 149 28.169 71.657  2.077 1.00 32.60 A3
ATOM 1107 H    ALA 149 27.662 72.424  2.411 1.00  0.00 A3
ATOM 1108 CA   ALA 149 27.890 71.134  0.757 1.00 32.70 A3
ATOM 1109 CB   ALA 149 26.595 71.774  0.299 1.00 31.91 A3
ATOM 1110 C    ALA 149 29.032 71.381 -0.258 1.00 33.75 A3
ATOM 1111 O    ALA 149 29.208 70.661 -1.264 1.00 34.49 A3
ATOM 1112 N    GLY 150 29.867 72.401 -0.052 1.00 33.58 A3
ATOM 1113 H    GLY 150 29.724 73.035  0.682 1.00  0.00 A3
ATOM 1114 CA   GLY 150 31.017 72.608 -0.913 1.00 31.79 A3

ATOM 1115 C    GLY 150 32.113 71.629 -0.478 1.00 31.39 A3
ATOM 1116 O    GLY 150 32.997 71.261 -1.265 1.00 31.77 A3
ATOM 1117 N    GLY 151 32.075 71.161  0.773 1.00 29.83 A3
ATOM 1118 H    GLY 151 31.412 71.524  1.394 1.00  0.00 A3
ATOM 1119 CA   GLY 151 33.018 70.166  1.243 1.00 32.16 A3
ATOM 1120 C    GLY 151 32.764 68.909  0.409 1.00 33.98 A3
ATOM 1121 O    GLY 151 33.664 68.501 -0.349 1.00 35.66 A3
ATOM 1122 N    VAL 152 31.486 68.418  0.451 1.00 31.87 A3
ATOM 1123 H    VAL 152 30.867 68.906  1.040 1.00  0.00 A3
ATOM 1124 CA   VAL 152 30.978 67.240 -0.275 1.00 29.61 A3
ATOM 1125 CB   VAL 152 29.419 67.145 -0.125 1.00 27.63 A3
ATOM 1126 CG1  VAL 152 28.883 66.035 -0.976 1.00 27.37 A3
ATOM 1127 CG2  VAL 152 29.002 66.786  1.279 1.00 24.74 A3
ATOM 1128 C    VAL 152 31.351 67.294 -1.762 1.00 29.91 A3
ATOM 1129 O    VAL 152 31.805 66.329 -2.393 1.00 31.75 A3
ATOM 1130 N    LEU 153 31.236 68.452 -2.361 1.00 29.26 A3
ATOM 1131 H    LEU 153 30.881 69.219 -1.860 1.00  0.00 A3
ATOM 1132 CA   LEU 153 31.559 68.607 -3.756 1.00 26.77 A3
ATOM 1133 CB   LEU 153 30.881 69.858 -4.160 1.00 28.22 A3
ATOM 1134 CG   LEU 153 29.943 69.894 -5.316 1.00 30.67 A3
ATOM 1135 CD1  LEU 153 28.580 69.281 -5.090 1.00 26.48 A3
ATOM 1136 CD2  LEU 153 29.741 71.365 -5.496 1.00 34.46 A3
ATOM 1137 C    LEU 153 33.032 68.628 -4.111 1.00 26.08 A3
ATOM 1138 O    LEU 153 33.419 68.187 -5.212 1.00 26.78 A3
ATOM 1139 N    VAL 154 33.902 69.180 -3.269 1.00 26.12 A3
ATOM 1140 H    VAL 154 33.589 69.557 -2.416 1.00  0.00 A3
ATOM 1141 CA   VAL 154 35.330 69.259 -3.611 1.00 26.23 A3
ATOM 1142 CB   VAL 154 36.057 70.299 -2.692 1.00 26.51 A3
ATOM 1143 CG1  VAL 154 37.578 70.188 -2.942 1.00 25.01 A3
ATOM 1144 CG2  VAL 154 35.528 71.728 -2.945 1.00 27.82 A3
ATOM 1145 C    VAL 154 35.933 67.850 -3.375 1.00 26.80 A3
ATOM 1146 O    VAL 154 36.678 67.363 -4.229 1.00 26.27 A3
ATOM 1147 N    ALA 155 35.635 67.241 -2.199 1.00 24.76 A3
ATOM 1148 H    ALA 155 35.084 67.758 -1.570 1.00  0.00 A3
ATOM 1149 CA   ALA 155 36.095 65.940 -1.782 1.00 25.21 A3
ATOM 1150 CB   ALA 155 35.463 65.572 -0.457 1.00 25.25 A3
```

FIG.5P

FIG.5Q

ATOM	1151	C	ALA	155	35.708	64.946	-2.841	1.00	26.94	A3
ATOM	1152	O	ALA	155	36.594	64.288	-3.398	1.00	26.76	A3
ATOM	1153	N	SER	156	34.450	64.982	-3.282	1.00	29.96	A3
ATOM	1154	H	SER	156	33.790	65.577	-2.868	1.00	0.00	A3
ATOM	1155	CA	SER	156	34.034	64.105	-4.354	1.00	32.17	A3
ATOM	1156	CB	SER	156	32.531	64.319	-4.544	1.00	34.23	A3
ATOM	1157	OG	SER	156	32.000	64.195	-5.879	1.00	39.35	A3
ATOM	1158	HG	SER	156	31.120	63.815	-5.851	1.00	0.00	A3
ATOM	1159	C	SER	156	34.845	64.338	-5.632	1.00	33.46	A3
ATOM	1160	O	SER	156	35.411	63.380	-6.174	1.00	34.62	A3
ATOM	1161	N	HIS	157	35.054	65.576	-6.133	1.00	33.90	A3
ATOM	1162	H	HIS	157	34.771	66.349	-5.605	1.00	0.00	A3
ATOM	1163	CA	HIS	157	35.821	65.773	-7.383	1.00	31.19	A3
ATOM	1164	CB	HIS	157	35.707	67.209	-7.900	1.00	32.59	A3
ATOM	1165	CG	HIS	157	34.369	67.449	-8.566	1.00	31.11	A3
ATOM	1166	CD2	HIS	157	34.127	67.394	-9.928	1.00	30.78	A3
ATOM	1167	ND1	HIS	157	33.223	67.666	-7.942	1.00	32.36	A3
ATOM	1168	HD1	HIS	157	33.080	67.773	-6.979	1.00	0.00	A3
ATOM	1169	CE1	HIS	157	32.293	67.732	-8.875	1.00	32.01	A3
ATOM	1170	NE2	HIS	157	32.838	67.571	-10.060	1.00	29.18	A3
ATOM	1171	HE2	HIS	157	32.327	67.621	-10.895	1.00	0.00	A3
ATOM	1172	C	HIS	157	37.291	65.476	-7.269	1.00	29.68	A3
ATOM	1173	O	HIS	157	37.950	65.059	-8.219	1.00	29.65	A3
ATOM	1174	N	LEU	158	37.801	65.669	-6.071	1.00	29.24	A3
ATOM	1175	H	LEU	158	37.213	65.901	-5.326	1.00	0.00	A3
ATOM	1176	CA	LEU	158	39.216	65.479	-5.826	1.00	31.94	A3
ATOM	1177	CB	LEU	158	39.609	65.949	-4.373	1.00	28.66	A3
ATOM	1178	CG	LEU	158	41.008	65.751	-3.859	1.00	24.32	A3
ATOM	1179	CD1	LEU	158	41.990	66.378	-4.776	1.00	20.87	A3
ATOM	1180	CD2	LEU	158	41.099	66.330	-2.477	1.00	24.86	A3
ATOM	1181	C	LEU	158	39.468	63.994	-6.027	1.00	31.46	A3
ATOM	1182	O	LEU	158	40.298	63.609	-6.844	1.00	30.58	A3
ATOM	1183	N	GLN	159	38.652	63.225	-5.340	1.00	33.54	A3
ATOM	1184	H	GLN	159	38.011	63.676	-4.748	1.00	0.00	A3
ATOM	1185	CA	GLN	159	38.594	61.792	-5.442	1.00	35.73	A3
ATOM	1186	CB	GLN	159	37.308	61.492	-4.813	1.00	37.26	A3
ATOM	1187	CG	GLN	159	37.064	60.063	-4.520	1.00	45.01	A3
ATOM	1188	CD	GLN	159	37.755	59.611	-3.256	1.00	46.24	A3
ATOM	1189	OE1	GLN	159	38.142	58.443	-3.232	1.00	48.29	A3
ATOM	1190	NE2	GLN	159	37.936	60.456	-2.224	1.00	47.82	A3
ATOM	1191	HE21	GLN	159	37.575	61.364	-2.289	1.00	0.00	A3
ATOM	1192	HE22	GLN	159	38.412	60.101	-1.447	1.00	0.00	A3
ATOM	1193	C	GLN	159	38.686	61.381	-6.921	1.00	36.24	A3
ATOM	1194	O	GLN	159	39.632	60.690	-7.324	1.00	38.97	A3
ATOM	1195	N	SER	160	37.824	61.896	-7.796	1.00	35.48	A3
ATOM	1196	H	SER	160	37.142	62.540	-7.498	1.00	0.00	A3
ATOM	1197	CA	SER	160	37.869	61.564	-9.203	1.00	34.96	A3
ATOM	1198	CB	SER	160	36.645	62.100	-9.863	1.00	37.54	A3
ATOM	1199	OG	SER	160	35.587	62.434	-8.942	1.00	44.81	A3
ATOM	1200	HG	SER	160	35.340	61.689	-8.387	1.00	0.00	A3
ATOM	1201	C	SER	160	39.090	62.095	-9.922	1.00	34.65	A3
ATOM	1202	O	SER	160	39.605	61.382	-10.785	1.00	35.42	A3
ATOM	1203	N	PHE	161	39.615	63.293	-9.595	1.00	33.82	A3
ATOM	1204	H	PHE	161	39.203	63.796	-8.864	1.00	0.00	A3
ATOM	1205	CA	PHE	161	40.820	63.850	-10.218	1.00	31.21	A3
ATOM	1206	CB	PHE	161	41.110	65.264	-9.629	1.00	28.28	A3
ATOM	1207	CG	PHE	161	42.455	65.881	-10.062	1.00	24.92	A3
ATOM	1208	CD1	PHE	161	42.696	66.228	-11.389	1.00	22.98	A3
ATOM	1209	CD2	PHE	161	43.464	66.021	-9.135	1.00	23.03	A3
ATOM	1210	CE1	PHE	161	43.941	66.695	-11.767	1.00	21.06	A3
ATOM	1211	CE2	PHE	161	44.701	66.495	-9.528	1.00	20.28	A3
ATOM	1212	CZ	PHE	161	44.939	66.826	-10.832	1.00	17.03	A3
ATOM	1213	C	PHE	161	42.008	62.907	-9.943	1.00	31.77	A3
ATOM	1214	O	PHE	161	42.786	62.578	-10.845	1.00	32.63	A3
ATOM	1215	N	LEU	162	42.117	62.434	-8.690	1.00	31.67	A3
ATOM	1216	H	LEU	162	41.420	62.691	-8.054	1.00	0.00	A3
ATOM	1217	CA	LEU	162	43.186	61.574	-8.232	1.00	31.29	A3
ATOM	1218	CB	LEU	162	43.204	61.433	-6.743	1.00	25.84	A3
ATOM	1219	CG	LEU	162	43.693	62.674	-6.003	1.00	26.02	A3
ATOM	1220	CD1	LEU	162	43.594	62.455	-4.516	1.00	25.24	A3
ATOM	1221	CD2	LEU	162	45.107	62.994	-6.415	1.00	27.04	A3
ATOM	1222	C	LEU	162	43.061	60.212	-8.813	1.00	34.23	A3

FIG. 5R

ATOM	1223	O	LEU	162	44.107	59.654	-9.070	1.00	36.51	A3
ATOM	1224	N	GLU	163	41.926	59.589	-9.082	1.00	37.24	A3
ATOM	1225	H	GLU	163	41.072	60.002	-8.826	1.00	0.00	A3
ATOM	1226	CA	GLU	163	41.975	58.327	-9.771	1.00	40.47	A3
ATOM	1227	CB	GLU	163	40.566	57.716	-9.835	1.00	45.38	A3
ATOM	1228	CG	GLU	163	40.264	56.975	-8.526	1.00	51.84	A3
ATOM	1229	CD	GLU	163	41.291	55.889	-8.126	1.00	57.97	A3
ATOM	1230	OE1	GLU	163	40.897	54.722	-8.092	1.00	62.01	A3
ATOM	1231	OE2	GLU	163	42.466	56.180	-7.832	1.00	59.17	A3
ATOM	1232	C	GLU	163	42.586	58.430	-11.142	1.00	41.34	A3
ATOM	1233	O	GLU	163	43.456	57.633	-11.486	1.00	42.17	A3
ATOM	1234	N	VAL	164	42.257	59.436	-11.920	1.00	42.28	A3
ATOM	1235	H	VAL	164	41.589	60.091	-11.615	1.00	0.00	A3
ATOM	1236	CA	VAL	164	42.911	59.609	-13.187	1.00	44.13	A3
ATOM	1237	CB	VAL	164	42.207	60.711	-13.940	1.00	45.52	A3
ATOM	1238	CG1	VAL	164	42.892	60.975	-15.278	1.00	48.79	A3
ATOM	1239	CG2	VAL	164	40.786	60.269	-14.226	1.00	46.09	A3
ATOM	1240	C	VAL	164	44.386	59.933	-12.991	1.00	46.13	A3
ATOM	1241	O	VAL	164	45.192	59.473	-13.794	1.00	45.99	A3
ATOM	1242	N	SER	165	44.879	60.677	-12.006	1.00	49.51	A3
ATOM	1243	H	SER	165	44.287	61.173	-11.396	1.00	0.00	A3
ATOM	1244	CA	SER	165	46.325	60.845	-11.895	1.00	53.44	A3
ATOM	1245	CB	SER	165	46.715	61.796	-10.775	1.00	54.77	A3
ATOM	1246	OG	SER	165	46.049	61.618	-9.530	1.00	59.99	A3
ATOM	1247	HG	SER	165	45.997	60.694	-9.261	1.00	0.00	A3
ATOM	1248	C	SER	165	46.958	59.502	-11.630	1.00	55.15	A3
ATOM	1249	O	SER	165	48.028	59.227	-12.148	1.00	55.02	A3
ATOM	1250	N	TYR	166	46.239	58.645	-10.900	1.00	58.57	A3
ATOM	1251	H	TYR	166	45.374	58.948	-10.549	1.00	0.00	A3
ATOM	1252	CA	TYR	166	46.617	57.273	-10.625	1.00	61.42	A3
ATOM	1253	CB	TYR	166	45.543	56.653	-9.680	1.00	64.05	A3
ATOM	1254	CG	TYR	166	45.502	55.138	-9.682	1.00	69.00	A3
ATOM	1255	CD1	TYR	166	44.389	54.501	-10.185	1.00	71.64	A3
ATOM	1256	CE1	TYR	166	44.367	53.130	-10.283	1.00	73.15	A3
ATOM	1257	CD2	TYR	166	46.594	54.409	-9.257	1.00	71.27	A3
ATOM	1258	CE2	TYR	166	46.584	53.040	-9.346	1.00	72.92	A3
ATOM	1259	CZ	TYR	166	45.468	52.417	-9.862	1.00	75.71	A3
ATOM	1260	OH	TYR	166	45.474	51.038	-10.016	1.00	80.61	A3
ATOM	1261	HH	TYR	166	44.571	50.736	-10.134	1.00	0.00	A3
ATOM	1262	C	TYR	166	46.712	56.567	-11.987	1.00	62.34	A3
ATOM	1263	O	TYR	166	47.766	55.981	-12.282	1.00	63.25	A3
ATOM	1264	N	ALA	167	45.727	56.622	-12.884	1.00	61.27	A3
ATOM	1265	H	ALA	167	44.893	57.089	-12.678	1.00	0.00	A3
ATOM	1266	CA	ALA	167	45.933	55.982	-14.159	1.00	61.47	A3
ATOM	1267	CB	ALA	167	44.608	55.904	-14.904	1.00	60.98	A3
ATOM	1268	C	ALA	167	46.982	56.694	-15.020	1.00	62.19	A3
ATOM	1269	O	ALA	167	47.719	56.000	-15.734	1.00	62.63	A3
ATOM	1270	N	VAL	168	47.210	58.011	-14.991	1.00	63.37	A3
ATOM	1271	H	VAL	168	46.756	58.570	-14.330	1.00	0.00	A3
ATOM	1272	CA	VAL	168	48.174	58.593	-15.923	1.00	65.62	A3
ATOM	1273	CB	VAL	168	48.061	60.121	-16.131	1.00	66.30	A3
ATOM	1274	CG1	VAL	168	46.687	60.431	-16.706	1.00	66.78	A3
ATOM	1275	CG2	VAL	168	48.278	60.879	-14.840	1.00	68.47	A3
ATOM	1276	C	VAL	168	49.579	58.339	-15.469	1.00	66.45	A3
ATOM	1277	O	VAL	168	50.458	58.183	-16.302	1.00	66.22	A3
ATOM	1278	N	LEU	169	49.823	58.241	-14.177	1.00	68.83	A3
ATOM	1279	H	LEU	169	49.102	58.404	-13.536	1.00	0.00	A3
ATOM	1280	CA	LEU	169	51.141	57.899	-13.695	1.00	71.81	A3
ATOM	1281	CB	LEU	169	51.249	58.228	-12.188	1.00	71.53	A3
ATOM	1282	CG	LEU	169	51.137	59.732	-11.813	1.00	70.68	A3
ATOM	1283	CD1	LEU	169	51.187	59.826	-10.298	1.00	69.39	A3
ATOM	1284	CD2	LEU	169	52.223	60.580	-12.491	1.00	68.49	A3
ATOM	1285	C	LEU	169	51.333	56.414	-13.979	1.00	73.61	A3
ATOM	1286	O	LEU	169	52.408	56.013	-14.429	1.00	74.75	A3
ATOM	1287	N	ARG	170	50.309	55.583	-13.819	1.00	75.45	A3
ATOM	1288	H	ARG	170	49.488	55.923	-13.399	1.00	0.00	A3
ATOM	1289	CA	ARG	170	50.364	54.179	-14.199	1.00	78.17	A3
ATOM	1290	CB	ARG	170	48.944	53.642	-14.004	1.00	78.45	A3
ATOM	1291	CG	ARG	170	48.394	52.506	-14.871	1.00	78.17	A3
ATOM	1292	CD	ARG	170	48.744	51.181	-14.271	1.00	77.25	A3
ATOM	1293	NE	ARG	170	48.123	51.120	-12.970	1.00	76.15	A3
ATOM	1294	HE	ARG	170	47.245	51.528	-12.824	1.00	0.00	A3

FIG.5S.

```
ATOM 1295 CZ   ARG 170  48.758 50.547 -11.970 1.00 76.14 A3
ATOM 1296 NH1  ARG 170  49.973 50.017 -12.112 1.00 76.84 A3
ATOM 1297 HH11 ARG 170  50.441 50.030 -12.994 1.00  0.00 A3
ATOM 1298 HH12 ARG 170  50.406 49.570 -11.329 1.00  0.00 A3
ATOM 1299 NH2  ARG 170  48.147 50.492 -10.806 1.00 77.02 A3
ATOM 1300 HH21 ARG 170  47.237 50.890 -10.714 1.00  0.00 A3
ATOM 1301 HH22 ARG 170  48.586 50.052 -10.023 1.00  0.00 A3
ATOM 1302 C    ARG 170  50.870 54.052 -15.647 1.00 79.84 A3
ATOM 1303 O    ARG 170  51.924 53.470 -15.908 1.00 80.07 A3
ATOM 1304 N    HIS 171  50.193 54.663 -16.611 1.00 81.38 A3
ATOM 1305 H    HIS 171  49.433 55.234 -16.359 1.00  0.00 A3
ATOM 1306 CA   HIS 171  50.663 54.597 -17.970 1.00 84.03 A3
ATOM 1307 CB   HIS 171  49.590 55.054 -18.902 1.00 86.82 A3
ATOM 1308 CG   HIS 171  48.496 54.037 -19.147 1.00 90.73 A3
ATOM 1309 CD2  HIS 171  47.467 53.765 -18.272 1.00 91.35 A3
ATOM 1310 ND1  HIS 171  48.308 53.301 -20.248 1.00 92.24 A3
ATOM 1311 HD1  HIS 171  48.887 53.287 -21.044 1.00  0.00 A3
ATOM 1312 CE1  HIS 171  47.204 52.605 -20.077 1.00 92.41 A3
ATOM 1313 NE2  HIS 171  46.711 52.892 -18.891 1.00 92.59 A3
ATOM 1314 HE2  HIS 171  45.884 52.511 -18.518 1.00  0.00 A3
ATOM 1315 C    HIS 171  51.907 55.446 -18.232 1.00 85.42 A3
ATOM 1316 O    HIS 171  52.440 55.352 -19.344 1.00 85.98 A3
ATOM 1317 N    LEU 172  52.359 56.307 -17.302 1.00 86.13 A3
ATOM 1318 H    LEU 172  51.870 56.411 -16.463 1.00  0.00 A3
ATOM 1319 CA   LEU 172  53.550 57.133 -17.496 1.00 86.02 A3
ATOM 1320 CB   LEU 172  53.500 58.357 -16.607 1.00 86.31 A3
ATOM 1321 CG   LEU 172  54.022 59.658 -17.203 1.00 87.48 A3
ATOM 1322 CD1  LEU 172  53.436 59.939 -18.596 1.00 87.68 A3
ATOM 1323 CD2  LEU 172  53.645 60.778 -16.251 1.00 87.95 A3
ATOM 1324 C    LEU 172  54.813 56.357 -17.180 1.00 85.92 A3
ATOM 1325 O    LEU 172  55.896 56.660 -17.692 1.00 86.23 A3
ATOM 1326 N    ALA 173  54.733 55.383 -16.282 1.00 85.49 A3
ATOM 1327 H    ALA 173  53.899 55.276 -15.769 1.00  0.00 A3
ATOM 1328 CA   ALA 173  55.856 54.497 -16.087 1.00 85.65 A3
ATOM 1329 CB   ALA 173  56.602 54.859 -14.809 1.00 85.01 A3
ATOM 1330 C    ALA 173  55.330 53.073 -16.008 1.00 86.54 A3

ATOM 1331 OT1  ALA 173  55.585 52.347 -16.971 1.00 87.21 A3
ATOM 1332 OT2  ALA 173  54.650 52.707 -15.036 1.00 87.31 A3
ATOM 1333 CB   LEU 210  45.234 42.591 25.453 1.00 52.47 B1
ATOM 1334 CG   LEU 210  43.799 42.058 25.547 1.00 51.68 B1
ATOM 1335 CD1  LEU 210  43.123 42.562 26.804 1.00 53.37 B1
ATOM 1336 CD2  LEU 210  43.050 42.453 24.303 1.00 51.37 B1
ATOM 1337 C    LEU 210  46.770 44.374 24.596 1.00 50.98 B1
ATOM 1338 O    LEU 210  46.475 45.267 23.790 1.00 51.76 B1
ATOM 1339 HT1  LEU 210  44.382 44.922 24.421 1.00  0.00 B1
ATOM 1340 HT2  LEU 210  45.157 45.974 25.414 1.00  0.00 B1
ATOM 1341 N    LEU 210  44.705 45.041 25.406 1.00 53.59 B1
ATOM 1342 HT3  LEU 210  43.855 45.012 25.997 1.00  0.00 B1
ATOM 1343 CA   LEU 210  45.730 44.038 25.676 1.00 52.35 B1
ATOM 1344 N    PRO 211  47.974 43.825 24.494 1.00 49.35 B1
ATOM 1345 CD   PRO 211  48.621 43.024 25.532 1.00 49.52 B1
ATOM 1346 CA   PRO 211  48.895 44.191 23.419 1.00 49.04 B1
ATOM 1347 CB   PRO 211  50.209 43.571 23.865 1.00 49.02 B1
ATOM 1348 CG   PRO 211  49.794 42.438 24.783 1.00 49.77 B1
ATOM 1349 C    PRO 211  48.543 43.864 21.965 1.00 48.03 B1
ATOM 1350 O    PRO 211  47.872 42.896 21.622 1.00 49.05 B1
ATOM 1351 N    GLN 212  49.032 44.675 21.051 1.00 46.52 B1
ATOM 1352 H    GLN 212  49.506 45.478 21.349 1.00  0.00 B1
ATOM 1353 CA   GLN 212  48.839 44.461 19.641 1.00 45.47 B1
ATOM 1354 CB   GLN 212  49.533 45.522 18.849 1.00 46.81 B1
ATOM 1355 CG   GLN 212  48.482 46.139 17.999 1.00 49.55 B1
ATOM 1356 CD   GLN 212  49.024 46.703 16.709 1.00 54.21 B1
ATOM 1357 OE1  GLN 212  48.429 47.672 16.232 1.00 57.72 B1
ATOM 1358 NE2  GLN 212  50.086 46.176 16.074 1.00 52.39 B1
ATOM 1359 HE21 GLN 212  50.530 45.383 16.430 1.00  0.00 B1
ATOM 1360 HE22 GLN 212  50.341 46.625 15.244 1.00  0.00 B1
ATOM 1361 C    GLN 212  49.390 43.133 19.185 1.00 44.79 B1
ATOM 1362 O    GLN 212  48.959 42.520 18.208 1.00 44.01 B1
ATOM 1363 N    SER 213  50.401 42.671 19.893 1.00 44.72 B1
ATOM 1364 H    SER 213  50.730 43.115 20.698 1.00  0.00 B1
ATOM 1365 CA   SER 213  51.025 41.424 19.521 1.00 43.76 B1
ATOM 1366 CB   SER 213  52.220 41.124 20.354 1.00 45.29 B1
```

FIG.5T

```
ATOM 1367 OG  SER 213  51.802 41.455 21.681 1.00 52.50 B1
ATOM 1368 HG  SER 213  52.479 41.127 22.288 1.00  0.00 B1
ATOM 1369 C   SER 213  50.014 40.376 19.784 1.00 40.92 B1
ATOM 1370 O   SER 213  49.964 39.492 18.947 1.00 43.32 B1
ATOM 1371 N   PHE 214  49.242 40.571 20.876 1.00 38.86 B1
ATOM 1372 H   PHE 214  49.414 41.370 21.410 1.00  0.00 B1
ATOM 1373 CA  PHE 214  48.210 39.664 21.336 1.00 37.40 B1
ATOM 1374 CB  PHE 214  47.568 40.064 22.634 1.00 37.45 B1
ATOM 1375 CG  PHE 214  46.494 39.080 23.035 1.00 41.01 B1
ATOM 1376 CD1 PHE 214  45.176 39.459 23.044 1.00 42.77 B1
ATOM 1377 CD2 PHE 214  46.818 37.794 23.400 1.00 42.02 B1
ATOM 1378 CE1 PHE 214  44.197 38.554 23.423 1.00 41.82 B1
ATOM 1379 CE2 PHE 214  45.834 36.898 23.776 1.00 41.70 B1
ATOM 1380 CZ  PHE 214  44.519 37.277 23.791 1.00 41.05 B1
ATOM 1381 C   PHE 214  47.109 39.656 20.321 1.00 36.54 B1
ATOM 1382 O   PHE 214  46.735 38.566 19.889 1.00 37.99 B1
ATOM 1383 N   LEU 215  46.616 40.812 19.893 1.00 33.27 B1
ATOM 1384 H   LEU 215  47.008 41.642 20.238 1.00  0.00 B1
ATOM 1385 CA  LEU 215  45.504 40.864 18.966 1.00 30.38 B1
ATOM 1386 CB  LEU 215  45.099 42.282 18.701 1.00 31.82 B1
ATOM 1387 CG  LEU 215  43.857 42.530 17.893 1.00 32.78 B1
ATOM 1388 CD1 LEU 215  42.727 41.963 18.737 1.00 32.95 B1
ATOM 1389 CD2 LEU 215  43.688 44.011 17.508 1.00 28.93 B1
ATOM 1390 C   LEU 215  45.811 40.232 17.648 1.00 29.57 B1
ATOM 1391 O   LEU 215  44.922 39.632 17.055 1.00 31.28 B1
ATOM 1392 N   LEU 216  47.031 40.379 17.155 1.00 29.44 B1
ATOM 1393 H   LEU 216  47.677 40.935 17.646 1.00  0.00 B1
ATOM 1394 CA  LEU 216  47.465 39.790 15.893 1.00 29.89 B1
ATOM 1395 CB  LEU 216  48.791 40.150 15.472 1.00 28.61 B1
ATOM 1396 CG  LEU 216  48.682 41.877 14.939 1.00 26.83 B1
ATOM 1397 CD1 LEU 216  49.925 42.558 15.344 1.00 28.57 B1
ATOM 1398 CD2 LEU 216  48.446 41.950 13.452 1.00 24.09 B1
ATOM 1399 C   LEU 216  47.613 38.274 16.062 1.00 31.23 B1
ATOM 1400 O   LEU 216  47.328 37.514 15.138 1.00 29.20 B1
ATOM 1401 N   LYS 217  47.999 37.826 17.261 1.00 32.50 B1
ATOM 1402 H   LYS 217  48.305 38.482 17.926 1.00  0.00 B1

ATOM 1403 CA  LYS 217  48.067 36.439 17.599 1.00 34.90 B1
ATOM 1404 CB  LYS 217  48.645 36.280 19.002 1.00 38.07 B1
ATOM 1405 CG  LYS 217  49.394 34.978 19.109 1.00 45.25 B1
ATOM 1406 CD  LYS 217  49.714 34.491 20.521 1.00 53.27 B1
ATOM 1407 CE  LYS 217  50.229 33.024 20.297 1.00 59.03 B1
ATOM 1408 NZ  LYS 217  50.213 32.135 21.467 1.00 62.10 B1
ATOM 1409 HZ1 LYS 217  49.239 32.056 21.824 1.00  0.00 B1
ATOM 1410 HZ2 LYS 217  50.830 32.515 22.214 1.00  0.00 B1
ATOM 1411 HZ3 LYS 217  50.554 31.195 21.179 1.00  0.00 B1
ATOM 1412 C   LYS 217  46.617 35.950 17.546 1.00 36.77 B1
ATOM 1413 O   LYS 217  46.311 34.933 16.886 1.00 39.58 B1
ATOM 1414 N   CYS 218  45.664 36.638 18.177 1.00 34.86 B1
ATOM 1415 H   CYS 218  45.907 37.388 18.751 1.00  0.00 B1
ATOM 1416 CA  CYS 218  44.277 36.238 18.076 1.00 33.61 B1
ATOM 1417 CB  CYS 218  43.430 37.175 18.846 1.00 33.21 B1
ATOM 1418 SG  CYS 218  43.856 36.710 20.515 1.00 35.92 B1
ATOM 1419 C   CYS 218  43.766 36.189 16.652 1.00 32.89 B1
ATOM 1420 O   CYS 218  43.155 35.169 16.323 1.00 34.71 B1
ATOM 1421 N   LEU 219  44.035 37.169 15.777 1.00 29.52 B1
ATOM 1422 H   LEU 219  44.512 37.960 16.104 1.00  0.00 B1
ATOM 1423 CA  LEU 219  43.614 37.119 14.393 1.00 27.44 B1
ATOM 1424 CB  LEU 219  44.116 38.412 13.727 1.00 26.24 B1
ATOM 1425 CG  LEU 219  43.884 38.768 12.241 1.00 25.07 B1
ATOM 1426 CD1 LEU 219  42.402 38.975 11.996 1.00 26.24 B1
ATOM 1427 CD2 LEU 219  44.563 40.051 11.882 1.00 22.10 B1
ATOM 1428 C   LEU 219  44.121 35.867 13.634 1.00 28.24 B1
ATOM 1429 O   LEU 219  43.373 35.204 12.889 1.00 27.12 B1
ATOM 1430 N   GLU 220  45.399 35.499 13.795 1.00 28.06 B1
ATOM 1431 H   GLU 220  45.957 35.974 14.448 1.00  0.00 B1
ATOM 1432 CA  GLU 220  45.963 34.411 13.048 1.00 28.38 B1
ATOM 1433 CB  GLU 220  47.376 34.198 13.469 1.00 34.25 B1
ATOM 1434 CG  GLU 220  48.049 33.079 12.666 1.00 46.36 B1
ATOM 1435 CD  GLU 220  49.545 32.794 12.907 1.00 55.51 B1
ATOM 1436 OE1 GLU 220  50.113 32.133 12.021 1.00 58.95 B1
ATOM 1437 OE2 GLU 220  50.144 33.213 13.930 1.00 60.41 B1
ATOM 1438 C   GLU 220  45.134 33.193 13.354 1.00 27.30 B1
```

FIG.5U

					x	y	z	occ	B	
ATOM	1439	O	GLU	220	44.662	32.524	12.437	1.00	27.08	B1
ATOM	1440	N	GLN	221	44.866	33.023	14.642	1.00	25.42	B1
ATOM	1441	H	GLN	221	45.229	33.687	15.268	1.00	0.00	B1
ATOM	1442	CA	GLN	221	44.074	31.940	15.176	1.00	26.28	B1
ATOM	1443	CB	GLN	221	44.143	31.927	16.691	1.00	26.78	B1
ATOM	1444	CG	GLN	221	45.555	31.456	17.011	1.00	29.19	B1
ATOM	1445	CD	GLN	221	45.752	31.067	18.442	1.00	31.98	B1
ATOM	1446	OE1	GLN	221	46.472	30.162	18.808	1.00	35.98	B1
ATOM	1447	NE2	GLN	221	45.110	31.736	19.347	1.00	39.31	B1
ATOM	1448	HE21	GLN	221	45.263	31.423	20.246	1.00	0.00	B1
ATOM	1449	HE22	GLN	221	44.571	32.514	19.111	1.00	0.00	B1
ATOM	1450	C	GLN	221	42.615	31.925	14.789	1.00	26.21	B1
ATOM	1451	O	GLN	221	42.186	30.896	14.269	1.00	30.69	B1
ATOM	1452	N	VAL	222	41.814	32.962	14.984	1.00	23.63	B1
ATOM	1453	H	VAL	222	42.199	33.746	15.426	1.00	0.00	B1
ATOM	1454	CA	VAL	222	40.429	33.034	14.537	1.00	21.92	B1
ATOM	1455	CB	VAL	222	39.934	34.442	14.793	1.00	21.36	B1
ATOM	1456	CG1	VAL	222	38.706	34.831	14.027	1.00	17.72	B1
ATOM	1457	CG2	VAL	222	39.671	34.496	16.257	1.00	20.95	B1
ATOM	1458	C	VAL	222	40.374	32.707	13.066	1.00	22.65	B1
ATOM	1459	O	VAL	222	39.475	32.013	12.632	1.00	23.72	B1
ATOM	1460	N	ARG	223	41.341	33.120	12.283	1.00	23.95	B1
ATOM	1461	H	ARG	223	42.099	33.614	12.666	1.00	0.00	B1
ATOM	1462	CA	ARG	223	41.309	32.939	10.844	1.00	27.19	B1
ATOM	1463	CB	ARG	223	42.294	33.935	10.283	1.00	29.26	B1
ATOM	1464	CG	ARG	223	42.102	34.364	8.869	1.00	35.23	B1
ATOM	1465	CD	ARG	223	42.880	33.487	7.929	1.00	41.88	B1
ATOM	1466	NE	ARG	223	41.972	32.676	7.096	1.00	47.42	B1
ATOM	1467	HE	ARG	223	41.451	31.953	7.502	1.00	0.00	B1
ATOM	1468	CZ	ARG	223	41.875	32.896	5.784	1.00	46.15	B1
ATOM	1469	NH1	ARG	223	42.575	33.837	5.246	1.00	49.54	B1
ATOM	1470	HH11	ARG	223	42.522	33.989	4.259	1.00	0.00	B1
ATOM	1471	HH12	ARG	223	43.156	34.428	5.805	1.00	0.00	B1
ATOM	1472	NH2	ARG	223	41.178	32.161	4.952	1.00	45.74	B1
ATOM	1473	HH21	ARG	223	40.697	31.353	5.290	1.00	0.00	B1
ATOM	1474	HH22	ARG	223	41.154	32.399	3.980	1.00	0.00	B1
ATOM	1475	C	ARG	223	41.624	31.492	10.430	1.00	29.13	B1
ATOM	1476	O	ARG	223	41.181	30.987	9.376	1.00	29.32	B1
ATOM	1477	N	LYS	224	42.413	30.791	11.259	1.00	29.17	B1
ATOM	1478	H	LYS	224	42.791	31.235	12.048	1.00	0.00	B1
ATOM	1479	CA	LYS	224	42.714	29.411	10.994	1.00	27.70	B1
ATOM	1480	CB	LYS	224	43.922	29.085	11.818	1.00	30.07	B1
ATOM	1481	CG	LYS	224	44.372	27.660	11.706	1.00	36.70	B1
ATOM	1482	CD	LYS	224	45.829	27.544	12.127	1.00	41.68	B1
ATOM	1483	CE	LYS	224	46.303	26.478	11.131	1.00	48.18	B1
ATOM	1484	NZ	LYS	224	47.750	26.492	10.913	1.00	53.57	B1
ATOM	1485	HZ1	LYS	224	48.230	26.241	11.801	1.00	0.00	B1
ATOM	1486	HZ2	LYS	224	48.057	27.436	10.606	1.00	0.00	B1
ATOM	1487	HZ3	LYS	224	47.998	25.792	10.183	1.00	0.00	B1
ATOM	1488	C	LYS	224	41.464	28.598	11.347	1.00	26.27	B1
ATOM	1489	O	LYS	224	40.970	27.810	10.510	1.00	24.82	B1
ATOM	1490	N	ILE	225	40.892	28.835	12.547	1.00	24.75	B1
ATOM	1491	H	ILE	225	41.308	29.487	13.151	1.00	0.00	B1
ATOM	1492	CA	ILE	225	39.656	28.147	12.943	1.00	23.33	B1
ATOM	1493	CB	ILE	225	39.146	28.622	14.296	1.00	18.08	B1
ATOM	1494	CG2	ILE	225	37.874	27.872	14.577	1.00	15.43	B1
ATOM	1495	CG1	ILE	225	40.161	28.400	15.380	1.00	13.38	B1
ATOM	1496	CD	ILE	225	39.787	28.967	16.749	1.00	13.59	B1
ATOM	1497	C	ILE	225	38.594	28.437	11.889	1.00	27.28	B1
ATOM	1498	O	ILE	225	37.978	27.492	11.400	1.00	31.49	B1
ATOM	1499	N	GLN	226	38.396	29.677	11.402	1.00	29.69	B1
ATOM	1500	H	GLN	226	38.894	30.413	11.803	1.00	0.00	B1
ATOM	1501	CA	GLN	226	37.450	29.969	10.313	1.00	29.12	B1
ATOM	1502	CB	GLN	226	37.366	31.438	9.962	1.00	32.26	B1
ATOM	1503	CG	GLN	226	36.682	32.156	11.108	1.00	36.28	B1
ATOM	1504	CD	GLN	226	36.429	33.613	10.816	1.00	37.88	B1
ATOM	1505	OE1	GLN	226	37.158	34.281	10.076	1.00	36.34	B1
ATOM	1506	NE2	GLN	226	35.359	34.114	11.421	1.00	39.62	B1
ATOM	1507	HE21	GLN	226	34.823	33.501	11.971	1.00	0.00	B1
ATOM	1508	HE22	GLN	226	35.153	35.057	11.287	1.00	0.00	B1
ATOM	1509	C	GLN	226	37.714	29.295	9.007	1.00	26.82	B1
ATOM	1510	O	GLN	226	36.775	28.887	8.325	1.00	27.45	B1

FIG.5V

```
ATOM 1511 N   GLY 227  38.940 29.186  8.570 1.00 26.55 B1
ATOM 1512 H   GLY 227  39.688 29.612  9.043 1.00  0.00 B1
ATOM 1513 CA  GLY 227  39.195 28.427  7.348 1.00 27.27 B1
ATOM 1514 C   GLY 227  38.832 26.949  7.574 1.00 27.65 B1
ATOM 1515 O   GLY 227  38.287 26.291  6.656 1.00 26.79 B1
ATOM 1516 N   ASP 228  39.025 26.429  8.819 1.00 27.03 B1
ATOM 1517 H   ASP 228  39.460 26.957  9.523 1.00  0.00 B1
ATOM 1518 CA  ASP 228  38.618 25.038  9.052 1.00 28.20 B1
ATOM 1519 CB  ASP 228  38.986 24.492 10.391 1.00 26.04 B1
ATOM 1520 CG  ASP 228  40.427 24.554 10.774 1.00 24.88 B1
ATOM 1521 OD1 ASP 228  40.627 24.521 11.977 1.00 23.37 B1
ATOM 1522 OD2 ASP 228  41.302 24.637  9.912 1.00 23.32 B1
ATOM 1523 C   ASP 228  37.120 24.830  8.992 1.00 27.23 B1
ATOM 1524 O   ASP 228  36.662 23.900  8.336 1.00 27.07 B1
ATOM 1525 N   GLY 229  36.390 25.739  9.639 1.00 26.74 B1
ATOM 1526 H   GLY 229  36.861 26.444 10.134 1.00  0.00 B1
ATOM 1527 CA  GLY 229  34.946 25.723  9.673 1.00 25.87 B1
ATOM 1528 C   GLY 229  34.393 25.825  8.274 1.00 24.95 B1
ATOM 1529 O   GLY 229  33.370 25.222  7.956 1.00 25.73 B1
ATOM 1530 N   ALA 230  35.058 26.541  7.391 1.00 23.97 B1
ATOM 1531 H   ALA 230  35.871 27.026  7.654 1.00  0.00 B1
ATOM 1532 CA  ALA 230  34.530 26.688  6.061 1.00 25.94 B1
ATOM 1533 CB  ALA 230  35.193 27.852  5.312 1.00 19.76 B1
ATOM 1534 C   ALA 230  34.794 25.403  5.304 1.00 29.42 B1
ATOM 1535 O   ALA 230  34.014 25.061  4.423 1.00 32.07 B1
ATOM 1536 N   ALA 231  35.878 24.671  5.572 1.00 32.16 B1
ATOM 1537 H   ALA 231  36.556 25.045  6.175 1.00  0.00 B1
ATOM 1538 CA  ALA 231  36.141 23.364  4.957 1.00 31.99 B1
ATOM 1539 CB  ALA 231  37.489 22.847  5.428 1.00 32.77 B1
ATOM 1540 C   ALA 231  35.060 22.361  5.386 1.00 32.99 B1
ATOM 1541 O   ALA 231  34.599 21.575  4.576 1.00 34.12 B1
ATOM 1542 N   LEU 232  34.662 22.309  6.652 1.00 33.30 B1
ATOM 1543 H   LEU 232  35.174 22.861  7.284 1.00  0.00 B1
ATOM 1544 CA  LEU 232  33.558 21.506  7.165 1.00 35.33 B1
ATOM 1545 CB  LEU 232  33.279 21.783  8.626 1.00 34.22 B1
ATOM 1546 CG  LEU 232  32.410 20.861  9.394 1.00 33.16 B1
ATOM 1547 CD1 LEU 232  33.191 19.545  9.451 1.00 34.59 B1
ATOM 1548 CD2 LEU 232  32.107 21.381 10.800 1.00 31.32 B1
ATOM 1549 C   LEU 232  32.271 21.829  6.440 1.00 36.65 B1
ATOM 1550 O   LEU 232  31.703 20.986  5.749 1.00 36.42 B1
ATOM 1551 N   GLN 233  31.836 23.084  6.570 1.00 38.89 B1
ATOM 1552 H   GLN 233  32.378 23.719  7.087 1.00  0.00 B1
ATOM 1553 CA  GLN 233  30.637 23.579  5.933 1.00 40.02 B1
ATOM 1554 CB  GLN 233  30.572 25.072  6.162 1.00 42.25 B1
ATOM 1555 CG  GLN 233  30.290 25.398  7.626 1.00 48.22 B1
ATOM 1556 CD  GLN 233  30.021 26.879  7.983 1.00 53.75 B1
ATOM 1557 OE1 GLN 233  30.799 27.810  7.718 1.00 55.93 B1
ATOM 1558 NE2 GLN 233  28.909 27.215  8.634 1.00 56.51 B1
ATOM 1559 HE21 GLN 233 28.810 28.144  8.902 1.00  0.00 B1
ATOM 1560 HE22 GLN 233 28.205 26.533  8.710 1.00  0.00 B1
ATOM 1561 C   GLN 233  30.635 23.243  4.441 1.00 39.70 B1
ATOM 1562 O   GLN 233  29.631 22.777  3.898 1.00 40.20 B1
ATOM 1563 N   GLU 234  31.744 23.377  3.736 1.00 39.32 B1
ATOM 1564 H   GLU 234  32.544 23.750  4.163 1.00  0.00 B1
ATOM 1565 CA  GLU 234  31.809 23.025  2.329 1.00 39.23 B1
ATOM 1566 CB  GLU 234  33.155 23.434  1.811 1.00 40.25 B1
ATOM 1567 CG  GLU 234  33.292 23.028  0.383 1.00 47.69 B1
ATOM 1568 CD  GLU 234  34.733 23.056 -0.073 1.00 53.40 B1
ATOM 1569 OE1 GLU 234  34.986 23.721 -1.100 1.00 53.78 B1
ATOM 1570 OE2 GLU 234  35.568 22.400  0.590 1.00 57.55 B1
ATOM 1571 C   GLU 234  31.580 21.535  2.136 1.00 37.09 B1
ATOM 1572 O   GLU 234  30.884 21.217  1.188 1.00 36.67 B1
ATOM 1573 N   LYS 235  32.092 20.623  2.986 1.00 37.27 B1
ATOM 1574 H   LYS 235  32.668 20.965  3.706 1.00  0.00 B1
ATOM 1575 CA  LYS 235  31.832 19.177  2.942 1.00 36.27 B1
ATOM 1576 CB  LYS 235  32.516 18.365  3.997 1.00 34.92 B1
ATOM 1577 CG  LYS 235  33.978 18.483  4.107 1.00 38.47 B1
ATOM 1578 CD  LYS 235  34.762 17.999  2.921 1.00 38.07 B1
ATOM 1579 CE  LYS 235  36.192 18.051  3.460 1.00 39.15 B1
ATOM 1580 NZ  LYS 235  37.117 17.460  2.521 1.00 41.34 B1
ATOM 1581 HZ1 LYS 235  37.080 17.978  1.622 1.00  0.00 B1
ATOM 1582 HZ2 LYS 235  36.854 16.466  2.363 1.00  0.00 B1
```

FIG.5M

```
ATOM 1583 HZ3 LYS 235  38.080 17.497  2.911 1.00  0.00 B1
ATOM 1584 C   LYS 235  30.363 18.847  3.204 1.00 35.20 B1
ATOM 1585 O   LYS 235  29.722 18.102  2.463 1.00 35.60 B1
ATOM 1586 N   LEU 236  29.807 19.332  4.301 1.00 33.53 B1
ATOM 1587 H   LEU 236  30.363 19.888  4.885 1.00  0.00 B1
ATOM 1588 CA  LEU 236  28.417 19.116  4.641 1.00 32.30 B1
ATOM 1589 CB  LEU 236  28.093 19.918  5.894 1.00 28.85 B1
ATOM 1590 CG  LEU 236  28.791 19.441  7.148 1.00 28.23 B1
ATOM 1591 CD1 LEU 236  28.703 20.460  8.268 1.00 24.14 B1
ATOM 1592 CD2 LEU 236  28.132 18.163  7.587 1.00 26.66 B1
ATOM 1593 C   LEU 236  27.590 19.574  3.453 1.00 33.69 B1
ATOM 1594 O   LEU 236  26.691 18.849  3.064 1.00 35.13 B1
ATOM 1595 N   CYS 237  27.870 20.670  2.753 1.00 34.49 B1
ATOM 1596 H   CYS 237  28.611 21.251  3.025 1.00  0.00 B1
ATOM 1597 CA  CYS 237  27.064 21.016  1.606 1.00 34.95 B1
ATOM 1598 C   CYS 237  27.324 20.090  0.451 1.00 35.97 B1
ATOM 1599 O   CYS 237  26.360 19.573 -0.089 1.00 36.09 B1
ATOM 1600 CB  CYS 237  27.334 22.413  1.130 1.00 35.18 B1
ATOM 1601 SC  CYS 237  26.409 22.880 -0.365 1.00 36.40 B1
ATOM 1602 N   ALA 238  28.571 19.804  0.074 1.00 37.29 B1
ATOM 1603 H   ALA 238  29.324 20.158  0.591 1.00  0.00 B1
ATOM 1604 CA  ALA 238  28.841 18.973 -1.090 1.00 36.80 B1
ATOM 1605 CB  ALA 238  30.274 18.684 -1.403 1.00 37.35 B1
ATOM 1606 C   ALA 238  28.320 17.617 -0.911 1.00 36.49 B1
ATOM 1607 O   ALA 238  27.645 17.198 -1.809 1.00 36.54 B1
ATOM 1608 N   THR 239  28.628 16.969  0.193 1.00 38.80 B1
ATOM 1609 H   THR 239  29.236 17.391  0.821 1.00  0.00 B1
ATOM 1610 CA  THR 239  28.230 15.587  0.464 1.00 41.33 B1
ATOM 1611 CB  THR 239  29.158 15.035  1.554 1.00 42.38 B1
ATOM 1612 OG1 THR 239  30.473 15.265  1.031 1.00 45.70 B1
ATOM 1613 HG1 THR 239  31.019 15.668  1.709 1.00  0.00 B1
ATOM 1614 CG2 THR 239  28.936 13.574  1.916 1.00 41.85 B1
ATOM 1615 C   THR 239  26.771 15.341  0.864 1.00 41.94 B1
ATOM 1616 O   THR 239  26.260 14.284  0.460 1.00 43.34 B1
ATOM 1617 N   TYR 240  26.095 16.207  1.669 1.00 40.07 B1
ATOM 1618 H   TYR 240  26.538 17.034  1.953 1.00  0.00 B1
ATOM 1619 CA  TYR 240  24.718 15.992  2.084 1.00 38.21 B1
ATOM 1620 CB  TYR 240  24.594 15.993  3.618 1.00 38.08 B1
ATOM 1621 CG  TYR 240  25.524 14.926  4.193 1.00 43.37 B1
ATOM 1622 CD1 TYR 240  26.475 15.243  5.149 1.00 45.06 B1
ATOM 1623 CE1 TYR 240  27.420 14.283  5.529 1.00 47.35 B1
ATOM 1624 CD2 TYR 240  25.518 13.643  3.641 1.00 43.89 B1
ATOM 1625 CE2 TYR 240  26.442 12.690  4.003 1.00 44.77 B1
ATOM 1626 CZ  TYR 240  27.410 13.005  4.943 1.00 47.96 B1
ATOM 1627 OH  TYR 240  28.390 12.047  5.244 1.00 46.59 B1
ATOM 1628 HH  TYR 240  28.027 11.187  4.992 1.00  0.00 B1
ATOM 1629 C   TYR 240  23.781 17.032  1.516 1.00 39.49 B1
ATOM 1630 O   TYR 240  22.587 16.934  1.775 1.00 42.76 B1
ATOM 1631 N   LYS 241  24.174 18.011  0.694 1.00 37.36 B1
ATOM 1632 H   LYS 241  25.091 18.023  0.345 1.00  0.00 B1
ATOM 1633 CA  LYS 241  23.314 19.115  0.275 1.00 36.37 B1
ATOM 1634 CB  LYS 241  22.173 18.648 -0.595 1.00 38.38 B1
ATOM 1635 CG  LYS 241  22.645 17.940 -1.838 1.00 42.94 B1
ATOM 1636 CD  LYS 241  23.468 18.809 -2.737 1.00 46.97 B1
ATOM 1637 CE  LYS 241  23.657 18.070 -4.051 1.00 49.20 B1
ATOM 1638 NZ  LYS 241  22.509 18.372 -4.893 1.00 51.54 B1
ATOM 1639 HZ1 LYS 241  22.447 19.400 -5.038 1.00  0.00 B1
ATOM 1640 HZ2 LYS 241  21.641 18.041 -4.426 1.00  0.00 B1
ATOM 1641 HZ3 LYS 241  22.609 17.895 -5.811 1.00  0.00 B1
ATOM 1642 C   LYS 241  22.720 19.904  1.429 1.00 33.37 B1
ATOM 1643 O   LYS 241  21.728 20.580  1.223 1.00 33.90 B1
ATOM 1644 N   LEU 242  23.286 19.853  2.648 1.00 31.40 B1
ATOM 1645 H   LEU 242  24.055 19.260  2.756 1.00  0.00 B1
ATOM 1646 CA  LEU 242  22.904 20.682  3.758 1.00 31.09 B1
ATOM 1647 CB  LEU 242  23.253 20.059  5.096 1.00 28.55 B1
ATOM 1648 CG  LEU 242  22.571 18.798  5.641 1.00 30.36 B1
ATOM 1649 CD1 LEU 242  22.530 18.814  7.138 1.00 29.62 B1
ATOM 1650 CD2 LEU 242  21.086 18.861  5.443 1.00 31.94 B1
ATOM 1651 C   LEU 242  23.778 21.933  3.550 1.00 34.03 B1
ATOM 1652 O   LEU 242  24.903 22.027  4.058 1.00 35.53 B1
ATOM 1653 N   CYS 243  23.316 22.883  2.722 1.00 34.89 B1
ATOM 1654 H   CYS 243  22.491 22.665  2.238 1.00  0.00 B1
```

FIG.5X

ATOM	1655	CA	CYS	243	24.051	24.083	2.377	1.00	35.42	B1
ATOM	1656	C	CYS	243	23.492	25.335	2.975	1.00	36.85	B1
ATOM	1657	O	CYS	243	23.956	26.400	2.565	1.00	40.10	B1
ATOM	1658	CB	CYS	243	24.046	24.383	0.929	1.00	33.12	B1
ATOM	1659	SG	CYS	243	24.438	22.883	0.099	1.00	38.25	B1
ATOM	1660	N	HIS	244	22.496	25.393	3.848	1.00	35.37	B1
ATOM	1661	H	HIS	244	22.185	24.588	4.318	1.00	0.00	B1
ATOM	1662	CA	HIS	244	21.939	26.676	4.191	1.00	33.29	B1
ATOM	1663	CB	HIS	244	20.655	26.987	3.340	1.00	33.64	B1
ATOM	1664	CG	HIS	244	20.915	27.205	1.857	1.00	33.12	B1
ATOM	1665	CD2	HIS	244	20.288	26.584	0.814	1.00	37.29	B1
ATOM	1666	ND1	HIS	244	21.874	27.902	1.298	1.00	36.85	B1
ATOM	1667	HD1	HIS	244	22.648	28.281	1.778	1.00	0.00	B1
ATOM	1668	CE1	HIS	244	21.874	27.722	-0.013	1.00	35.95	B1
ATOM	1669	NE2	HIS	244	20.910	26.920	-0.301	1.00	35.54	B1
ATOM	1670	HE2	HIS	244	20.616	26.706	-1.214	1.00	0.00	B1
ATOM	1671	C	HIS	244	21.621	26.565	5.650	1.00	33.38	B1
ATOM	1672	O	HIS	244	20.546	26.105	6.029	1.00	33.23	B1
ATOM	1673	N	PRO	245	22.539	27.018	6.499	1.00	33.21	B1
ATOM	1674	CD	PRO	245	23.851	27.524	6.099	1.00	31.29	B1
ATOM	1675	CA	PRO	245	22.373	26.979	7.948	1.00	34.16	B1
ATOM	1676	CB	PRO	245	23.490	27.799	8.467	1.00	32.85	B1
ATOM	1677	CG	PRO	245	24.564	27.549	7.428	1.00	31.74	B1
ATOM	1678	C	PRO	245	21.032	27.470	8.407	1.00	36.26	B1
ATOM	1679	O	PRO	245	20.478	26.878	9.315	1.00	38.13	B1
ATOM	1680	N	GLU	246	20.529	28.463	7.640	1.00	39.64	B1
ATOM	1681	H	GLU	246	21.134	28.747	6.934	1.00	0.00	B1
ATOM	1682	CA	GLU	246	19.257	29.229	7.711	1.00	41.10	B1
ATOM	1683	CB	GLU	246	19.044	30.107	6.438	1.00	43.15	B1
ATOM	1684	CG	GLU	246	20.256	30.918	5.944	1.00	47.07	B1
ATOM	1685	CD	GLU	246	20.813	30.539	4.558	1.00	52.63	B1
ATOM	1686	OE1	GLU	246	22.054	30.545	4.374	1.00	54.22	B1
ATOM	1687	OE2	GLU	246	20.002	30.250	3.656	1.00	53.39	B1
ATOM	1688	C	GLU	246	18.071	28.298	7.819	1.00	40.57	B1
ATOM	1689	O	GLU	246	17.308	28.338	8.791	1.00	39.90	B1
ATOM	1690	N	GLU	247	18.025	27.388	6.840	1.00	40.32	B1
ATOM	1691	H	GLU	247	18.750	27.334	6.190	1.00	0.00	B1
ATOM	1692	CA	GLU	247	17.001	26.347	6.830	1.00	40.76	B1
ATOM	1693	CB	GLU	247	17.139	25.423	5.642	1.00	44.03	B1
ATOM	1694	CG	GLU	247	16.830	26.240	4.400	1.00	48.54	B1
ATOM	1695	CD	GLU	247	17.163	25.628	3.050	1.00	50.24	B1
ATOM	1696	OE1	GLU	247	16.849	26.299	2.056	1.00	52.92	B1
ATOM	1697	OE2	GLU	247	17.744	24.533	2.987	1.00	50.84	B1
ATOM	1698	C	GLU	247	16.966	25.444	8.034	1.00	39.24	B1
ATOM	1699	O	GLU	247	15.915	24.888	8.329	1.00	39.40	B1
ATOM	1700	N	LEU	248	18.066	25.280	8.760	1.00	37.92	B1
ATOM	1701	H	LEU	248	18.864	25.814	8.576	1.00	0.00	B1
ATOM	1702	CA	LEU	248	18.101	24.338	9.858	1.00	35.75	B1
ATOM	1703	CB	LEU	248	19.458	23.623	9.796	1.00	34.13	B1
ATOM	1704	CG	LEU	248	19.669	22.866	8.430	1.00	34.00	B1
ATOM	1705	CD1	LEU	248	20.997	22.149	8.306	1.00	33.97	B1
ATOM	1706	CD2	LEU	248	18.620	21.810	8.322	1.00	32.33	B1
ATOM	1707	C	LEU	248	17.871	25.031	11.155	1.00	36.51	B1
ATOM	1708	O	LEU	248	17.736	24.370	12.186	1.00	36.31	B1
ATOM	1709	N	VAL	249	17.663	26.350	11.146	1.00	38.88	B1
ATOM	1710	H	VAL	249	17.566	26.810	10.283	1.00	0.00	B1
ATOM	1711	CA	VAL	249	17.573	27.133	12.371	1.00	41.39	B1
ATOM	1712	CB	VAL	249	17.265	28.640	12.020	1.00	43.72	B1
ATOM	1713	CG1	VAL	249	15.804	28.985	11.776	1.00	44.70	B1
ATOM	1714	CG2	VAL	249	17.702	29.434	13.214	1.00	45.20	B1
ATOM	1715	C	VAL	249	16.590	26.635	13.406	1.00	42.61	B1
ATOM	1716	O	VAL	249	16.912	26.716	14.594	1.00	44.77	B1
ATOM	1717	N	LEU	250	15.453	26.035	13.016	1.00	43.61	B1
ATOM	1718	H	LEU	250	15.319	25.919	12.053	1.00	0.00	B1
ATOM	1719	CA	LEU	250	14.457	25.537	13.987	1.00	43.96	B1
ATOM	1720	CB	LEU	250	13.102	25.296	13.373	1.00	43.88	B1
ATOM	1721	CG	LEU	250	12.729	26.281	12.313	1.00	47.04	B1
ATOM	1722	CD1	LEU	250	13.092	25.577	11.011	1.00	47.30	B1
ATOM	1723	CD2	LEU	250	11.286	26.772	12.441	1.00	46.18	B1
ATOM	1724	C	LEU	250	14.852	24.207	14.626	1.00	43.96	B1
ATOM	1725	O	LEU	250	14.450	23.887	15.764	1.00	44.07	B1
ATOM	1726	N	LEU	251	15.691	23.446	13.893	1.00	42.41	B1

FIG.5Y

```
ATOM 1727 H   LEU 251  16.049 23.788 13.048 1.00  0.00 B1
ATOM 1728 CA  LEU 251  16.155 22.159 14.362 1.00 40.63 B1
ATOM 1729 CB  LEU 251  16.834 21.418 13.257 1.00 36.17 B1
ATOM 1730 CG  LEU 251  15.996 20.629 12.267 1.00 33.16 B1
ATOM 1731 CD1 LEU 251  14.595 21.168 11.956 1.00 33.36 B1
ATOM 1732 CD2 LEU 251  16.875 20.619 11.050 1.00 34.71 B1
ATOM 1733 C   LEU 251  17.104 22.372 15.493 1.00 42.78 B1
ATOM 1734 O   LEU 251  17.124 21.554 16.395 1.00 45.44 B1
ATOM 1735 N   GLY 252  17.826 23.477 15.610 1.00 44.86 B1
ATOM 1736 H   GLY 252  17.750 24.160 14.910 1.00  0.00 B1
ATOM 1737 CA  GLY 252  18.734 23.711 16.719 1.00 46.68 B1
ATOM 1738 C   GLY 252  18.071 23.596 18.067 1.00 49.18 B1
ATOM 1739 O   GLY 252  18.709 23.318 19.077 1.00 49.23 B1
ATOM 1740 N   HIS 253  16.756 23.787 18.046 1.00 53.74 B1
ATOM 1741 H   HIS 253  16.358 24.055 17.190 1.00  0.00 B1
ATOM 1742 CA  HIS 253  15.859 23.649 19.197 1.00 57.46 B1
ATOM 1743 CB  HIS 253  14.468 24.157 18.764 1.00 62.93 B1
ATOM 1744 CG  HIS 253  13.212 23.813 19.577 1.00 68.75 B1
ATOM 1745 CD2 HIS 253  12.031 24.529 19.414 1.00 71.00 B1
ATOM 1746 ND1 HIS 253  12.980 22.854 20.479 1.00 70.67 B1
ATOM 1747 HD1 HIS 253  13.627 22.193 20.830 1.00  0.00 B1
ATOM 1748 CE1 HIS 253  11.723 22.966 20.845 1.00 73.40 B1
ATOM 1749 NE2 HIS 253  11.156 23.973 20.204 1.00 72.91 B1
ATOM 1750 HE2 HIS 253  10.218 24.260 20.311 1.00  0.00 B1
ATOM 1751 C   HIS 253  15.771 22.209 19.691 1.00 56.06 B1
ATOM 1752 O   HIS 253  15.880 21.827 20.857 1.00 56.17 B1
ATOM 1753 N   SER 254  15.395 21.435 18.724 1.00 53.46 B1
ATOM 1754 H   SER 254  15.278 21.783 17.813 1.00  0.00 B1
ATOM 1755 CA  SER 254  15.177 20.034 18.898 1.00 52.61 B1
ATOM 1756 CB  SER 254  14.613 19.595 17.576 1.00 53.04 B1
ATOM 1757 OG  SER 254  13.793 20.686 17.158 1.00 56.04 B1
ATOM 1758 HG  SER 254  13.369 20.467 16.319 1.00  0.00 B1
ATOM 1759 C   SER 254  16.512 19.386 19.275 1.00 51.48 B1
ATOM 1760 O   SER 254  16.596 18.639 20.245 1.00 51.90 B1
ATOM 1761 N   LEU 255  17.577 19.790 18.562 1.00 49.31 B1
ATOM 1762 H   LEU 255  17.430 20.480 17.889 1.00  0.00 B1

ATOM 1763 CA  LEU 255  18.913 19.272 18.723 1.00 46.02 B1
ATOM 1764 CB  LEU 255  19.706 19.723 17.537 1.00 44.66 B1
ATOM 1765 CG  LEU 255  19.362 18.968 16.274 1.00 44.51 B1
ATOM 1766 CD1 LEU 255  19.810 19.679 15.006 1.00 43.16 B1
ATOM 1767 CD2 LEU 255  19.969 17.604 16.456 1.00 44.67 B1
ATOM 1768 C   LEU 255  19.536 19.718 20.012 1.00 46.56 B1
ATOM 1769 O   LEU 255  20.565 19.174 20.440 1.00 46.82 B1
ATOM 1770 N   GLY 256  18.918 20.759 20.581 1.00 45.93 B1
ATOM 1771 H   GLY 256  18.210 21.225 20.101 1.00  0.00 B1
ATOM 1772 CA  GLY 256  19.277 21.273 21.890 1.00 46.68 B1
ATOM 1773 C   GLY 256  20.669 21.866 21.970 1.00 47.28 B1
ATOM 1774 O   GLY 256  21.273 21.844 23.056 1.00 49.64 B1
ATOM 1775 N   ILE 257  21.143 22.441 20.849 1.00 45.74 B1
ATOM 1776 H   ILE 257  20.497 22.589 20.128 1.00  0.00 B1
ATOM 1777 CA  ILE 257  22.481 23.017 20.726 1.00 43.64 B1
ATOM 1778 CB  ILE 257  22.684 23.363 19.257 1.00 42.54 B1
ATOM 1779 CG2 ILE 257  23.988 24.110 19.073 1.00 41.05 B1
ATOM 1780 CG1 ILE 257  22.694 22.088 18.437 1.00 40.55 B1
ATOM 1781 CD  ILE 257  22.452 22.468 16.970 1.00 39.49 B1
ATOM 1782 C   ILE 257  22.559 24.246 21.616 1.00 43.27 B1
ATOM 1783 O   ILE 257  21.706 25.110 21.450 1.00 43.22 B1
ATOM 1784 N   PRO 258  23.441 24.392 22.608 1.00 43.05 B1
ATOM 1785 CD  PRO 258  24.133 23.321 23.296 1.00 43.29 B1
ATOM 1786 CA  PRO 258  23.559 25.616 23.360 1.00 43.82 B1
ATOM 1787 CB  PRO 258  24.295 25.236 24.612 1.00 41.97 B1
ATOM 1788 CG  PRO 258  25.107 24.064 24.186 1.00 43.79 B1
ATOM 1789 C   PRO 258  24.252 26.703 22.555 1.00 46.06 B1
ATOM 1790 O   PRO 258  24.983 26.513 21.560 1.00 46.59 B1
ATOM 1791 N   TRP 259  23.996 27.887 23.106 1.00 46.75 B1
ATOM 1792 H   TRP 259  23.588 27.921 23.994 1.00  0.00 B1
ATOM 1793 CA  TRP 259  24.427 29.143 22.517 1.00 45.77 B1
ATOM 1794 CB  TRP 259  23.213 30.071 22.397 1.00 46.60 B1
ATOM 1795 CG  TRP 259  23.556 31.372 21.749 1.00 47.51 B1
ATOM 1796 CD2 TRP 259  23.860 31.525 20.430 1.00 47.83 B1
ATOM 1797 CE2 TRP 259  24.154 32.888 20.392 1.00 48.47 B1
ATOM 1798 CE3 TRP 259  23.940 30.745 19.290 1.00 47.39 B1
```

FIG.5Z

ATOM	1799	CD1	TRP	259	23.639	32.520	22.493	1.00 48.60	B1
ATOM	1800	NE1	TRP	259	24.013	33.421	21.628	1.00 48.27	B1
ATOM	1801	HE1	TRP	259	24.224	34.344	21.870	1.00 0.00	B1
ATOM	1802	CZ2	TRP	259	24.531	33.486	19.195	1.00 47.40	B1
ATOM	1803	CZ3	TRP	259	24.317	31.344	18.097	1.00 49.07	B1
ATOM	1804	CH2	TRP	259	24.613	32.706	18.050	1.00 49.12	B1
ATOM	1805	C	TRP	259	25.459	29.727	23.440	1.00 44.01	B1
ATOM	1806	O	TRP	259	25.340	29.664	24.671	1.00 43.25	B1
ATOM	1807	N	ALA	260	26.469	30.247	22.777	1.00 43.01	B1
ATOM	1808	H	ALA	260	26.523	30.198	21.796	1.00 0.00	B1
ATOM	1809	CA	ALA	260	27.493	30.973	23.482	1.00 43.48	B1
ATOM	1810	CB	ALA	260	28.874	30.549	22.969	1.00 43.33	B1
ATOM	1811	C	ALA	260	27.249	32.486	23.216	1.00 43.41	B1
ATOM	1812	O	ALA	260	27.315	32.946	22.054	1.00 40.55	B1
ATOM	1813	N	PRO	261	26.853	33.267	24.253	1.00 42.61	B1
ATOM	1814	CD	PRO	261	26.527	32.807	25.606	1.00 42.33	B1
ATOM	1815	CA	PRO	261	26.720	34.701	24.199	1.00 42.37	B1
ATOM	1816	CB	PRO	261	25.778	34.987	25.335	1.00 41.46	B1
ATOM	1817	CG	PRO	261	26.251	34.060	26.411	1.00 40.00	B1
ATOM	1818	C	PRO	261	28.087	35.369	24.311	1.00 42.22	B1
ATOM	1819	O	PRO	261	28.988	34.956	25.037	1.00 38.82	B1
ATOM	1820	N	LEU	262	28.234	36.403	23.486	1.00 45.20	B1
ATOM	1821	H	LEU	262	27.513	36.610	22.853	1.00 0.00	B1
ATOM	1822	CA	LEU	262	29.434	37.210	23.498	1.00 46.50	B1
ATOM	1823	CB	LEU	262	30.531	36.609	22.610	1.00 45.09	B1
ATOM	1824	CG	LEU	262	31.903	37.157	22.964	1.00 42.55	B1
ATOM	1825	CD1	LEU	262	32.344	36.695	24.338	1.00 41.52	B1
ATOM	1826	CD2	LEU	262	32.850	36.730	21.900	1.00 44.21	B1
ATOM	1827	C	LEU	262	29.154	38.628	23.035	1.00 48.56	B1
ATOM	1828	O	LEU	262	29.633	39.470	23.790	1.00 48.23	B1
ATOM	1829	N	SER	263	28.388	38.956	21.960	1.00 51.33	B1
ATOM	1830	H	SER	263	27.982	38.242	21.427	1.00 0.00	B1
ATOM	1831	CA	SER	263	28.127	40.339	21.494	1.00 55.19	B1
ATOM	1832	CB	SER	263	26.871	40.511	20.612	1.00 57.17	B1
ATOM	1833	OG	SER	263	26.498	39.411	19.776	1.00 64.12	B1
ATOM	1834	HG	SER	263	26.093	38.741	20.336	1.00 0.00	B1
ATOM	1835	C	SER	263	27.909	41.354	22.600	1.00 56.15	B1
ATOM	1836	O	SER	263	28.744	42.243	22.753	1.00 57.88	B1
ATOM	1837	N	SER	264	26.899	41.231	23.452	1.00 56.52	B1
ATOM	1838	H	SER	264	26.277	40.478	23.415	1.00 0.00	B1
ATOM	1839	CA	SER	264	26.716	42.204	24.494	1.00 58.28	B1
ATOM	1840	CB	SER	264	25.313	41.977	25.064	1.00 58.77	B1
ATOM	1841	OG	SER	264	25.099	40.726	25.713	1.00 58.50	B1
ATOM	1842	HG	SER	264	25.385	40.832	26.632	1.00 0.00	B1
ATOM	1843	C	SER	264	27.800	42.168	25.584	1.00 59.95	B1
ATOM	1844	O	SER	264	27.610	42.805	26.620	1.00 60.44	B1
ATOM	1845	N	CYS	265	28.948	41.484	25.466	1.00 61.37	B1
ATOM	1846	H	CYS	265	29.192	41.114	24.596	1.00 0.00	B1
ATOM	1847	CA	CYS	265	29.958	41.502	26.509	1.00 62.57	B1
ATOM	1848	CB	CYS	265	30.991	40.418	26.285	1.00 64.32	B1
ATOM	1849	SG	CYS	265	32.322	40.638	27.504	1.00 71.40	B1
ATOM	1850	C	CYS	265	30.667	42.860	26.515	1.00 63.12	B1
ATOM	1851	OT1	CYS	265	31.065	43.360	25.444	1.00 63.44	B1
ATOM	1852	OT2	CYS	265	30.809	43.408	27.610	1.00 61.72	B1
ATOM	1853	CB	ALA	272	40.020	43.327	30.788	1.00 77.44	B2
ATOM	1854	C	ALA	272	38.698	41.201	30.601	1.00 76.53	B2
ATOM	1855	O	ALA	272	37.525	40.873	30.361	1.00 76.81	B2
ATOM	1856	HT1	ALA	272	37.486	43.550	30.261	1.00 0.00	B2
ATOM	1857	HT2	ALA	272	37.357	42.450	28.996	1.00 0.00	B2
ATOM	1858	N	ALA	272	37.973	43.169	29.427	1.00 76.81	B2
ATOM	1859	HT3	ALA	272	38.195	43.924	28.752	1.00 0.00	B2
ATOM	1860	CA	ALA	272	39.176	42.460	29.853	1.00 77.02	B2
ATOM	1861	N	ALA	273	39.485	40.547	31.487	1.00 74.93	B2
ATOM	1862	H	ALA	273	40.334	40.963	31.745	1.00 0.00	B2
ATOM	1863	CA	ALA	273	39.244	39.241	32.119	1.00 72.64	B2
ATOM	1864	CB	ALA	273	39.704	39.279	33.558	1.00 71.92	B2
ATOM	1865	C	ALA	273	37.872	38.599	32.118	1.00 71.60	B2
ATOM	1866	O	ALA	273	37.806	37.458	31.702	1.00 71.68	B2
ATOM	1867	N	GLY	274	36.775	39.282	32.484	1.00 70.20	B2
ATOM	1868	H	GLY	274	36.903	40.167	32.874	1.00 0.00	B2
ATOM	1869	CA	GLY	274	35.412	38.758	32.425	1.00 66.78	B2
ATOM	1870	C	GLY	274	35.050	38.437	30.990	1.00 65.05	B2

FIG. 5AA

```
ATOM 1871 O   GLY 274  34.627 37.320 30.709 1.00 66.44  B2
ATOM 1872 N   CYS 275  35.301 39.364 30.048 1.00 62.77  B2
ATOM 1873 H   CYS 275  35.634 40.223 30.357 1.00 0.00   B2
ATOM 1874 CA  CYS 275  35.026 39.188 28.611 1.00 59.30  B2
ATOM 1875 C   CYS 275  35.875 38.063 28.054 1.00 55.89  B2
ATOM 1876 O   CYS 275  35.425 37.152 27.351 1.00 54.41  B2
ATOM 1877 CB  CYS 275  35.349 40.466 27.827 1.00 61.50  B2
ATOM 1878 SG  CYS 275  34.119 40.937 26.577 1.00 66.63  B2
ATOM 1879 N   LEU 276  37.124 38.114 28.506 1.00 52.23  B2
ATOM 1880 H   LEU 276  37.350 38.722 29.233 1.00 0.00   B2
ATOM 1881 CA  LEU 276  38.091 37.163 28.066 1.00 48.93  B2
ATOM 1882 CB  LEU 276  39.483 37.564 28.542 1.00 45.96  B2
ATOM 1883 CG  LEU 276  40.241 38.557 27.670 1.00 43.20  B2
ATOM 1884 CD1 LEU 276  41.599 38.782 28.279 1.00 44.63  B2
ATOM 1885 CD2 LEU 276  40.429 38.033 26.271 1.00 40.55  B2
ATOM 1886 C   LEU 276  37.673 35.833 28.638 1.00 47.84  B2
ATOM 1887 O   LEU 276  37.784 34.803 27.964 1.00 48.51  B2
ATOM 1888 N   ALA 277  37.074 35.840 29.804 1.00 45.56  B2
ATOM 1889 H   ALA 277  36.898 36.662 30.289 1.00 0.00   B2
ATOM 1890 CA  ALA 277  36.613 34.605 30.365 1.00 45.77  B2
ATOM 1891 CB  ALA 277  36.147 34.810 31.783 1.00 47.87  B2
ATOM 1892 C   ALA 277  35.442 34.111 29.542 1.00 45.03  B2
ATOM 1893 O   ALA 277  35.342 32.926 29.271 1.00 44.20  B2
ATOM 1894 N   GLN 278  34.592 35.000 29.049 1.00 45.13  B2
ATOM 1895 H   GLN 278  34.731 35.944 29.263 1.00 0.00   B2
ATOM 1896 CA  GLN 278  33.435 34.601 28.284 1.00 45.27  B2
ATOM 1897 CB  GLN 278  32.550 35.825 28.083 1.00 48.13  B2
ATOM 1898 CG  GLN 278  31.140 35.442 28.484 1.00 56.00  B2
ATOM 1899 CD  GLN 278  30.045 36.464 28.178 1.00 61.94  B2
ATOM 1900 OE1 GLN 278  29.048 36.530 28.896 1.00 65.95  B2
ATOM 1901 NE2 GLN 278  30.080 37.291 27.132 1.00 65.55  B2
ATOM 1902 HE21 GLN 278  30.829 37.221 26.510 1.00 0.00  B2
ATOM 1903 HE22 GLN 278  29.343 37.927 27.056 1.00 0.00  B2
ATOM 1904 C   GLN 278  33.812 33.971 26.950 1.00 43.16  B2
ATOM 1905 O   GLN 278  33.173 33.050 26.462 1.00 40.58  B2
ATOM 1906 N   LEU 279  34.869 34.476 26.331 1.00 43.32  B2

ATOM 1907 H   LEU 279  35.328 35.227 26.767 1.00 0.00   B2
ATOM 1908 CA  LEU 279  35.398 33.966 25.069 1.00 42.80  B2
ATOM 1909 CB  LEU 279  36.583 34.790 24.626 1.00 41.42  B2
ATOM 1910 CG  LEU 279  36.885 35.014 23.190 1.00 40.76  B2
ATOM 1911 CD1 LEU 279  38.239 35.647 23.130 1.00 41.76  B2
ATOM 1912 CD2 LEU 279  36.943 33.753 22.411 1.00 40.01  B2
ATOM 1913 C   LEU 279  35.876 32.554 25.341 1.00 42.92  B2
ATOM 1914 O   LEU 279  35.572 31.598 24.640 1.00 42.57  B2
ATOM 1915 N   HIS 280  36.654 32.463 26.403 1.00 43.93  B2
ATOM 1916 H   HIS 280  36.837 33.282 26.917 1.00 0.00   B2
ATOM 1917 CA  HIS 280  37.215 31.223 26.850 1.00 46.12  B2
ATOM 1918 CB  HIS 280  38.029 31.506 28.101 1.00 48.74  B2
ATOM 1919 CG  HIS 280  38.914 30.320 28.394 1.00 54.16  B2
ATOM 1920 CD2 HIS 280  40.041 30.069 27.650 1.00 56.02  B2
ATOM 1921 ND1 HIS 280  38.759 29.326 29.264 1.00 56.01  B2
ATOM 1922 HD1 HIS 280  38.012 29.203 29.890 1.00 0.00   B2
ATOM 1923 CE1 HIS 280  39.744 28.483 29.058 1.00 56.64  B2
ATOM 1924 NE2 HIS 280  40.507 28.937 28.088 1.00 56.64  B2
ATOM 1925 HE2 HIS 280  41.282 28.478 27.684 1.00 0.00   B2
ATOM 1926 C   HIS 280  36.161 30.134 27.117 1.00 45.65  B2
ATOM 1927 O   HIS 280  36.362 28.977 26.711 1.00 46.23  B2
ATOM 1928 N   SER 281  35.086 30.473 27.822 1.00 43.91  B2
ATOM 1929 H   SER 281  35.009 31.367 28.219 1.00 0.00   B2
ATOM 1930 CA  SER 281  34.008 29.574 28.105 1.00 43.53  B2
ATOM 1931 CB  SER 281  33.026 30.291 29.002 1.00 44.18  B2
ATOM 1932 OG  SER 281  33.761 30.812 30.113 1.00 47.79  B2
ATOM 1933 HG  SER 281  33.288 30.648 30.931 1.00 0.00   B2
ATOM 1934 C   SER 281  33.382 29.169 26.787 1.00 43.35  B2
ATOM 1935 O   SER 281  33.334 27.973 26.496 1.00 44.83  B2
ATOM 1936 N   GLY 282  32.977 30.120 25.940 1.00 42.33  B2
ATOM 1937 H   GLY 282  33.043 31.058 26.221 1.00 0.00   B2
ATOM 1938 CA  GLY 282  32.363 29.869 24.632 1.00 40.65  B2
ATOM 1939 C   GLY 282  33.175 28.937 23.755 1.00 39.06  B2
ATOM 1940 O   GLY 282  32.584 28.075 23.107 1.00 40.10  B2
ATOM 1941 N   LEU 283  34.514 29.066 23.776 1.00 37.39  B2
ATOM 1942 H   LEU 283  34.880 29.807 24.304 1.00 0.00   B2
```

FIG.5BB

```
ATOM 1943 CA  LEU 283  35.465 28.213 23.037 1.00 35.06 B2
ATOM 1944 CB  LEU 283  36.902 28.718 23.089 1.00 30.20 B2
ATOM 1945 CG  LEU 283  37.167 30.001 22.302 1.00 25.73 B2
ATOM 1946 CD1 LEU 283  38.539 30.461 22.664 1.00 24.38 B2
ATOM 1947 CD2 LEU 283  37.036 29.802 20.815 1.00 21.94 B2
ATOM 1948 C   LEU 283  35.470 26.851 23.651 1.00 34.81 B2
ATOM 1949 O   LEU 283  35.314 25.859 22.947 1.00 31.09 B2
ATOM 1950 N   PHE 284  35.533 26.842 24.973 1.00 37.62 B2
ATOM 1951 H   PHE 284  35.567 27.686 25.467 1.00 0.00  B2
ATOM 1952 CA  PHE 284  35.485 25.596 25.710 1.00 42.51 B2
ATOM 1953 CB  PHE 284  35.542 25.877 27.184 1.00 49.49 B2
ATOM 1954 CG  PHE 284  36.221 24.770 27.968 1.00 58.39 B2
ATOM 1955 CD1 PHE 284  37.265 25.108 28.816 1.00 63.05 B2
ATOM 1956 CD2 PHE 284  35.810 23.453 27.861 1.00 60.84 B2
ATOM 1957 CE1 PHE 284  37.900 24.124 29.563 1.00 65.86 B2
ATOM 1958 CE2 PHE 284  36.444 22.480 28.605 1.00 64.49 B2
ATOM 1959 CZ  PHE 284  37.486 22.810 29.455 1.00 66.32 B2
ATOM 1960 C   PHE 284  34.204 24.849 25.384 1.00 41.44 B2
ATOM 1961 O   PHE 284  34.257 23.630 25.306 1.00 41.42 B2
ATOM 1962 N   LEU 285  33.100 25.563 25.101 1.00 41.24 B2
ATOM 1963 H   LEU 285  33.192 26.534 25.174 1.00 0.00  B2
ATOM 1964 CA  LEU 285  31.781 25.025 24.730 1.00 38.92 B2
ATOM 1965 CB  LEU 285  30.727 26.139 24.807 1.00 39.05 B2
ATOM 1966 CG  LEU 285  29.292 25.740 24.481 1.00 41.16 B2
ATOM 1967 CD1 LEU 285  28.711 24.981 25.662 1.00 41.12 B2
ATOM 1968 CD2 LEU 285  28.472 26.971 24.139 1.00 39.60 B2
ATOM 1969 C   LEU 285  31.780 24.441 23.329 1.00 37.34 B2
ATOM 1970 O   LEU 285  31.245 23.351 23.095 1.00 36.97 B2
ATOM 1971 N   TYR 286  32.352 25.172 22.372 1.00 35.26 B2
ATOM 1972 H   TYR 286  32.705 26.062 22.593 1.00 0.00  B2
ATOM 1973 CA  TYR 286  32.455 24.660 21.033 1.00 35.04 B2
ATOM 1974 CB  TYR 286  32.891 25.790 20.122 1.00 34.44 B2
ATOM 1975 CG  TYR 286  31.690 26.684 19.808 1.00 34.75 B2
ATOM 1976 CD1 TYR 286  31.433 27.879 20.469 1.00 35.67 B2
ATOM 1977 CE1 TYR 286  30.313 28.620 20.158 1.00 36.90 B2
ATOM 1978 CD2 TYR 286  30.823 26.255 18.839 1.00 36.19 B2
ATOM 1979 CE2 TYR 286  29.707 26.990 18.521 1.00 37.55 B2
ATOM 1980 CZ  TYR 286  29.449 28.164 19.178 1.00 37.73 B2
ATOM 1981 OH  TYR 286  28.285 28.826 18.823 1.00 38.04 B2
ATOM 1982 HH  TYR 286  28.289 29.707 19.243 1.00 0.00  B2
ATOM 1983 C   TYR 286  33.393 23.464 20.926 1.00 34.80 B2
ATOM 1984 O   TYR 286  33.071 22.537 20.180 1.00 35.35 B2
ATOM 1985 N   ALA 287  34.527 23.339 21.636 1.00 34.66 B2
ATOM 1986 H   ALA 287  34.803 24.088 22.206 1.00 0.00  B2
ATOM 1987 CA  ALA 287  35.350 22.108 21.565 1.00 34.28 B2
ATOM 1988 CB  ALA 287  36.617 22.291 22.415 1.00 33.63 B2
ATOM 1989 C   ALA 287  34.528 20.906 22.073 1.00 33.32 B2
ATOM 1990 O   ALA 287  34.535 19.827 21.478 1.00 33.07 B2
ATOM 1991 N   GLY 288  33.723 21.118 23.111 1.00 33.19 B2
ATOM 1992 H   GLY 288  33.791 21.985 23.564 1.00 0.00  B2
ATOM 1993 CA  GLY 288  32.761 20.162 23.655 1.00 35.62 B2
ATOM 1994 C   GLY 288  31.744 19.606 22.636 1.00 36.89 B2
ATOM 1995 O   GLY 288  31.624 18.379 22.444 1.00 34.97 B2
ATOM 1996 N   LEU 289  31.037 20.536 21.966 1.00 36.69 B2
ATOM 1997 H   LEU 289  31.200 21.476 22.201 1.00 0.00  B2
ATOM 1998 CA  LEU 289  30.018 20.249 20.954 1.00 35.05 B2
ATOM 1999 CB  LEU 289  29.351 21.576 20.502 1.00 36.32 B2
ATOM 2000 CG  LEU 289  28.552 22.450 21.464 1.00 35.76 B2
ATOM 2001 CD1 LEU 289  28.256 23.821 20.890 1.00 32.66 B2
ATOM 2002 CD2 LEU 289  27.246 21.780 21.697 1.00 35.35 B2
ATOM 2003 C   LEU 289  30.536 19.519 19.714 1.00 34.21 B2
ATOM 2004 O   LEU 289  29.871 18.694 19.078 1.00 33.28 B2
ATOM 2005 N   LEU 290  31.756 19.902 19.355 1.00 33.25 B2
ATOM 2006 H   LEU 290  32.183 20.634 19.850 1.00 0.00  B2
ATOM 2007 CA  LEU 290  32.448 19.345 18.230 1.00 32.44 B2
ATOM 2008 CB  LEU 290  33.729 20.159 18.000 1.00 32.62 B2
ATOM 2009 CG  LEU 290  33.560 21.509 17.315 1.00 32.05 B2
ATOM 2010 CD1 LEU 290  34.889 22.189 17.349 1.00 32.58 B2
ATOM 2011 CD2 LEU 290  33.068 21.374 15.879 1.00 31.74 B2
ATOM 2012 C   LEU 290  32.737 17.908 18.558 1.00 31.94 B2
ATOM 2013 O   LEU 290  32.432 17.020 17.772 1.00 30.50 B2
ATOM 2014 N   GLN 291  33.249 17.711 19.770 1.00 33.58 B2
```

FIG.5CC

ATOM	2015	H	GLN	291	33.512	18.494	20.298	1.00	0.00	B2
ATOM	2016	CA	GLN	291	33.499	16.372	20.311	1.00	36.39	B2
ATOM	2017	CB	GLN	291	33.988	16.490	21.702	1.00	36.86	B2
ATOM	2018	CG	GLN	291	34.926	15.367	21.950	1.00	39.48	B2
ATOM	2019	CD	GLN	291	35.658	15.503	23.252	1.00	40.79	B2
ATOM	2020	OE1	GLN	291	36.457	14.626	23.549	1.00	44.80	B2
ATOM	2021	NE2	GLN	291	35.494	16.535	24.072	1.00	42.59	B2
ATOM	2022	HE21	GLN	291	34.928	17.287	23.817	1.00	0.00	B2
ATOM	2023	HE22	GLN	291	35.910	16.463	24.958	1.00	0.00	B2
ATOM	2024	C	GLN	291	32.233	15.536	20.307	1.00	36.66	B2
ATOM	2025	O	GLN	291	32.220	14.478	19.707	1.00	37.46	B2
ATOM	2026	N	ALA	292	31.143	16.023	20.913	1.00	38.37	B2
ATOM	2027	H	ALA	292	31.255	16.849	21.418	1.00	0.00	B2
ATOM	2028	CA	ALA	292	29.778	15.451	20.857	1.00	39.25	B2
ATOM	2029	CB	ALA	292	28.818	16.485	21.444	1.00	40.28	B2
ATOM	2030	C	ALA	292	29.215	14.999	19.484	1.00	38.65	B2
ATOM	2031	O	ALA	292	28.411	14.067	19.356	1.00	37.58	B2
ATOM	2032	N	LEU	293	29.614	15.702	18.430	1.00	39.00	B2
ATOM	2033	H	LEU	293	30.149	16.513	18.574	1.00	0.00	B2
ATOM	2034	CA	LEU	293	29.265	15.335	17.077	1.00	39.74	B2
ATOM	2035	CB	LEU	293	29.662	16.418	16.106	1.00	37.53	B2
ATOM	2036	CG	LEU	293	28.969	17.701	16.138	1.00	34.34	B2
ATOM	2037	CD1	LEU	293	29.547	18.582	15.053	1.00	33.88	B2
ATOM	2038	CD2	LEU	293	27.503	17.462	15.918	1.00	35.69	B2
ATOM	2039	C	LEU	293	29.933	14.060	16.596	1.00	40.86	B2
ATOM	2040	O	LEU	293	29.686	13.669	15.449	1.00	40.58	B2
ATOM	2041	N	GLU	294	30.887	13.495	17.365	1.00	42.12	B2
ATOM	2042	H	GLU	294	31.131	13.963	18.190	1.00	0.00	B2
ATOM	2043	CA	GLU	294	31.598	12.253	17.076	1.00	42.89	B2
ATOM	2044	CB	GLU	294	30.806	10.984	17.485	1.00	48.38	B2
ATOM	2045	CG	GLU	294	30.715	10.614	18.972	1.00	56.26	B2
ATOM	2046	CD	GLU	294	29.271	10.408	19.486	1.00	63.70	B2
ATOM	2047	OE1	GLU	294	29.058	10.603	20.702	1.00	67.72	B2
ATOM	2048	OE2	GLU	294	28.363	10.074	18.692	1.00	64.81	B2
ATOM	2049	C	GLU	294	31.972	12.068	15.632	1.00	41.53	B2
ATOM	2050	O	GLU	294	31.804	11.007	15.021	1.00	40.29	B2
ATOM	2051	N	GLY	295	32.424	13.203	15.106	1.00	40.93	B2
ATOM	2052	H	GLY	295	32.357	14.033	15.621	1.00	0.00	B2
ATOM	2053	CA	GLY	295	32.998	13.236	13.783	1.00	39.95	B2
ATOM	2054	C	GLY	295	32.027	13.230	12.634	1.00	40.60	B2
ATOM	2055	O	GLY	295	32.477	13.216	11.487	1.00	40.96	B2
ATOM	2056	N	ILE	296	30.728	13.296	12.898	1.00	41.18	B2
ATOM	2057	H	ILE	296	30.446	13.210	13.825	1.00	0.00	B2
ATOM	2058	CA	ILE	296	29.687	13.306	11.888	1.00	44.02	B2
ATOM	2059	CB	ILE	296	29.683	14.580	11.009	1.00	43.49	B2
ATOM	2060	CG2	ILE	296	28.288	14.685	10.421	1.00	40.56	B2
ATOM	2061	CG1	ILE	296	30.047	15.831	11.793	1.00	45.11	B2
ATOM	2062	CD	ILE	296	30.039	17.189	11.062	1.00	46.06	B2
ATOM	2063	C	ILE	296	29.820	12.107	10.949	1.00	46.71	B2
ATOM	2064	O	ILE	296	28.918	11.279	11.060	1.00	50.61	B2
ATOM	2065	N	SER	297	30.767	11.875	10.019	1.00	47.21	B2
ATOM	2066	H	SER	297	31.526	12.491	9.936	1.00	0.00	B2
ATOM	2067	CA	SER	297	30.810	10.646	9.234	1.00	46.73	B2
ATOM	2068	CB	SER	297	30.239	10.884	7.865	1.00	45.48	B2
ATOM	2069	OG	SER	297	30.988	11.782	7.072	1.00	46.27	B2
ATOM	2070	HG	SER	297	30.321	12.200	6.503	1.00	0.00	B2
ATOM	2071	C	SER	297	32.263	10.269	9.123	1.00	48.72	B2
ATOM	2072	O	SER	297	33.120	11.122	9.391	1.00	50.55	B2
ATOM	2073	N	PRO	298	32.655	9.069	8.697	1.00	49.68	B2
ATOM	2074	CD	PRO	298	31.782	7.964	8.334	1.00	50.62	B2
ATOM	2075	CA	PRO	298	34.049	8.701	8.458	1.00	50.33	B2
ATOM	2076	CB	PRO	298	33.948	7.308	7.856	1.00	51.53	B2
ATOM	2077	CG	PRO	298	32.576	7.266	7.231	1.00	50.43	B2
ATOM	2078	C	PRO	298	34.795	9.692	7.579	1.00	50.08	B2
ATOM	2079	O	PRO	298	35.883	10.137	7.930	1.00	50.50	B2
ATOM	2080	N	GLN	299	34.173	10.086	6.469	1.00	50.48	B2
ATOM	2081	H	GLN	299	33.279	9.729	6.296	1.00	0.00	B2
ATOM	2082	CA	GLN	299	34.749	11.050	5.550	1.00	51.74	B2
ATOM	2083	CB	GLN	299	33.898	11.236	4.301	1.00	54.33	B2
ATOM	2084	CG	GLN	299	33.095	10.067	3.725	1.00	58.11	B2
ATOM	2085	CD	GLN	299	31.658	10.086	4.259	1.00	61.49	B2
ATOM	2086	OE1	GLN	299	31.160	9.083	4.776	1.00	61.00	B2

FIG.5DD

ATOM 2087 NE2 GLN 299 30.942 11.217 4.204 1.00 62.12 B2
ATOM 2088 HE21 GLN 299 31.345 12.012 3.800 1.00 0.00 B2
ATOM 2089 HE22 GLN 299 30.034 11.191 4.566 1.00 0.00 B2
ATOM 2090 C GLN 299 34.923 12.453 6.160 1.00 51.04 B2
ATOM 2091 O GLN 299 35.796 13.186 5.718 1.00 53.38 B2
ATOM 2092 N LEU 300 34.118 12.918 7.120 1.00 48.15 B2
ATOM 2093 H LEU 300 33.383 12.351 7.437 1.00 0.00 B2
ATOM 2094 CA LEU 300 34.272 14.220 7.745 1.00 43.32 B2
ATOM 2095 CB LEU 300 32.856 14.719 8.021 1.00 41.39 B2
ATOM 2096 CG LEU 300 32.073 15.546 6.974 1.00 37.99 B2
ATOM 2097 CD1 LEU 300 31.872 14.824 5.688 1.00 38.34 B2
ATOM 2098 CD2 LEU 300 30.705 15.809 7.522 1.00 37.67 B2
ATOM 2099 C LEU 300 35.142 14.220 9.019 1.00 42.84 B2
ATOM 2100 O LEU 300 35.558 15.278 9.541 1.00 41.56 B2
ATOM 2101 N GLY 301 35.467 13.016 9.528 1.00 40.83 B2
ATOM 2102 H GLY 301 35.157 12.221 9.046 1.00 0.00 B2
ATOM 2103 CA GLY 301 36.199 12.826 10.779 1.00 38.72 B2
ATOM 2104 C GLY 301 37.500 13.607 10.887 1.00 37.69 B2
ATOM 2105 O GLY 301 37.665 14.406 11.809 1.00 37.31 B2
ATOM 2106 N PRO 302 38.468 13.452 9.985 1.00 37.33 B2
ATOM 2107 CD PRO 302 38.353 12.630 8.790 1.00 37.77 B2
ATOM 2108 CA PRO 302 39.676 14.281 9.884 1.00 37.60 B2
ATOM 2109 CB PRO 302 40.256 13.907 8.541 1.00 36.62 B2
ATOM 2110 CG PRO 302 39.047 13.487 7.745 1.00 37.94 B2
ATOM 2111 C PRO 302 39.486 15.782 10.033 1.00 37.45 B2
ATOM 2112 O PRO 302 40.132 16.398 10.901 1.00 38.33 B2
ATOM 2113 N THR 303 38.547 16.311 9.204 1.00 37.05 B2
ATOM 2114 H THR 303 38.085 15.727 8.567 1.00 0.00 B2
ATOM 2115 CA THR 303 38.119 17.705 9.128 1.00 35.81 B2
ATOM 2116 CB THR 303 36.963 17.770 8.123 1.00 37.26 B2
ATOM 2117 OG1 THR 303 37.416 17.161 6.909 1.00 39.64 B2
ATOM 2118 HG1 THR 303 37.369 17.785 6.178 1.00 0.00 B2
ATOM 2119 CG2 THR 303 36.469 19.204 7.927 1.00 38.55 B2
ATOM 2120 C THR 303 37.687 18.223 10.506 1.00 34.93 B2
ATOM 2121 O THR 303 38.085 19.263 11.063 1.00 35.11 B2
ATOM 2122 N LEU 304 36.928 17.366 11.150 1.00 33.76 B2

ATOM 2123 H LEU 304 36.672 16.500 10.762 1.00 0.00 B2
ATOM 2124 CA LEU 304 36.436 17.746 12.418 1.00 31.01 B2
ATOM 2125 CB LEU 304 35.345 16.803 12.708 1.00 30.31 B2
ATOM 2126 CG LEU 304 34.234 17.567 13.320 1.00 31.32 B2
ATOM 2127 CD1 LEU 304 33.121 17.626 12.309 1.00 28.87 B2
ATOM 2128 CD2 LEU 304 33.921 16.970 14.692 1.00 34.23 B2
ATOM 2129 C LEU 304 37.553 17.726 13.421 1.00 31.86 B2
ATOM 2130 O LEU 304 37.615 18.623 14.259 1.00 34.21 B2
ATOM 2131 N ASP 305 38.510 16.811 13.326 1.00 30.56 B2
ATOM 2132 H ASP 305 38.456 16.117 12.635 1.00 0.00 B2
ATOM 2133 CA ASP 305 39.576 16.797 14.303 1.00 30.72 B2
ATOM 2134 CB ASP 305 40.504 15.608 14.114 1.00 36.20 B2
ATOM 2135 CG ASP 305 39.912 14.201 14.288 1.00 40.64 B2
ATOM 2136 OD1 ASP 305 38.976 14.040 15.103 1.00 37.52 B2
ATOM 2137 OD2 ASP 305 40.426 13.304 13.581 1.00 42.39 B2
ATOM 2138 C ASP 305 40.435 18.034 14.238 1.00 27.56 B2
ATOM 2139 O ASP 305 40.775 18.575 15.311 1.00 24.61 B2
ATOM 2140 N THR 306 40.781 18.417 12.979 1.00 24.77 B2
ATOM 2141 H THR 306 40.469 17.875 12.230 1.00 0.00 B2
ATOM 2142 CA THR 306 41.553 19.633 12.751 1.00 24.39 B2
ATOM 2143 CB THR 306 41.665 19.931 11.318 1.00 24.58 B2
ATOM 2144 OG1 THR 306 42.074 18.753 10.665 1.00 25.13 B2
ATOM 2145 HG1 THR 306 41.447 18.029 10.768 1.00 -0.00 B2
ATOM 2146 CG2 THR 306 42.690 21.027 11.089 1.00 25.77 B2
ATOM 2147 C THR 306 40.893 20.844 13.419 1.00 25.24 B2
ATOM 2148 O THR 306 41.488 21.472 14.296 1.00 27.24 B2
ATOM 2149 N LEU 307 39.615 21.134 13.139 1.00 25.91 B2
ATOM 2150 H LEU 307 39.125 20.547 12.520 1.00 0.00 B2
ATOM 2151 CA LEU 307 38.900 22.228 13.764 1.00 25.53 B2
ATOM 2152 CB LEU 307 37.571 22.170 13.142 1.00 25.09 B2
ATOM 2153 CG LEU 307 36.530 23.097 13.588 1.00 27.93 B2
ATOM 2154 CD1 LEU 307 37.008 24.515 13.484 1.00 29.87 B2
ATOM 2155 CD2 LEU 307 35.311 22.846 12.728 1.00 28.93 B2
ATOM 2156 C LEU 307 38.850 22.214 15.269 1.00 27.09 B2
ATOM 2157 O LEU 307 38.854 23.253 15.925 1.00 30.03 B2
ATOM 2158 N GLN 308 38.875 21.044 15.879 1.00 29.09 B2

```
ATOM  2159 H    GLN  308   38.883 20.239 15.319 1.00  0.00     B2
ATOM  2160 CA   GLN  308   38.824 20.848 17.340 1.00 29.36     B2
ATOM  2161 CB   GLN  308   38.379 19.399 17.562 1.00 29.41     B2
ATOM  2162 CG   GLN  308   37.862 19.140 18.935 1.00 32.24     B2
ATOM  2163 CD   GLN  308   37.586 17.672 19.165 1.00 34.03     B2
ATOM  2164 OE1  GLN  308   36.973 17.023 18.311 1.00 33.48     B2
ATOM  2165 NE2  GLN  308   38.053 17.127 20.299 1.00 31.67     B2
ATOM  2166 HE21 GLN  308   38.547 17.697 20.917 1.00  0.00     B2
ATOM  2167 HE22 GLN  308   37.875 16.174 20.436 1.00  0.00     B2
ATOM  2168 C    GLN  308   40.154 21.138 18.051 1.00 28.94     B2
ATOM  2169 O    GLN  308   40.196 21.796 19.101 1.00 28.44     B2
ATOM  2170 N    LEU  309   41.269 20.671 17.460 1.00 28.78     B2
ATOM  2171 H    LEU  309   41.157 20.120 16.655 1.00  0.00     B2
ATOM  2172 CA   LEU  309   42.632 20.923 17.967 1.00 28.56     B2
ATOM  2173 CB   LEU  309   43.671 20.154 17.106 1.00 26.54     B2
ATOM  2174 CG   LEU  309   43.632 18.636 17.241 1.00 24.98     B2
ATOM  2175 CD1  LEU  309   44.595 17.935 16.353 1.00 24.17     B2
ATOM  2176 CD2  LEU  309   43.992 18.310 18.621 1.00 23.45     B2
ATOM  2177 C    LEU  309   42.893 22.416 17.909 1.00 28.24     B2
ATOM  2178 O    LEU  309   43.370 22.957 18.907 1.00 30.32     B2
ATOM  2179 N    ASP  310   42.548 23.027 16.749 1.00 26.58     B2
ATOM  2180 H    ASP  310   42.296 22.437 16.007 1.00  0.00     B2
ATOM  2181 CA   ASP  310   42.495 24.477 16.495 1.00 27.90     B2
ATOM  2182 CB   ASP  310   42.025 24.659 15.076 1.00 28.41     B2
ATOM  2183 CG   ASP  310   43.162 24.556 14.096 1.00 31.84     B2
ATOM  2184 OD1  ASP  310   42.959 24.766 12.905 1.00 31.54     B2
ATOM  2185 OD2  ASP  310   44.297 24.314 14.514 1.00 37.32     B2
ATOM  2186 C    ASP  310   41.666 25.410 17.422 1.00 27.99     B2
ATOM  2187 O    ASP  310   42.219 26.429 17.876 1.00 27.23     B2
ATOM  2188 N    VAL  311   40.374 25.086 17.725 1.00 26.29     B2
ATOM  2189 H    VAL  311   39.961 24.347 17.225 1.00  0.00     B2
ATOM  2190 CA   VAL  311   39.546 25.803 18.706 1.00 24.29     B2
ATOM  2191 CB   VAL  311   38.098 25.217 18.869 1.00 21.47     B2
ATOM  2192 CG1  VAL  311   37.341 25.915 19.949 1.00 19.01     B2
ATOM  2193 CG2  VAL  311   37.261 25.488 17.667 1.00 18.56     B2
ATOM  2194 C    VAL  311   40.270 25.638 20.020 1.00 27.21     B2

ATOM  2195 O    VAL  311   40.437 26.647 20.719 1.00 29.71     B2
ATOM  2196 N    ALA  312   40.762 24.428 20.357 1.00 27.97     B2
ATOM  2197 H    ALA  312   40.585 23.674 19.756 1.00  0.00     B2
ATOM  2198 CA   ALA  312   41.515 24.157 21.583 1.00 29.24     B2
ATOM  2199 CB   ALA  312   41.855 22.688 21.532 1.00 30.53     B2
ATOM  2200 C    ALA  312   42.778 25.026 21.784 1.00 30.06     B2
ATOM  2201 O    ALA  312   43.057 25.508 22.886 1.00 30.04     B2
ATOM  2202 N    ASP  313   43.554 25.286 20.735 1.00 31.33     B2
ATOM  2203 H    ASP  313   43.433 24.730 19.935 1.00  0.00     B2
ATOM  2204 CA   ASP  313   44.610 26.275 20.743 1.00 34.22     B2
ATOM  2205 CB   ASP  313   45.279 26.512 19.447 1.00 38.87     B2
ATOM  2206 CG   ASP  313   46.071 25.404 18.866 1.00 44.55     B2
ATOM  2207 OD1  ASP  313   46.225 25.439 17.636 1.00 48.67     B2
ATOM  2208 OD2  ASP  313   46.521 24.553 19.647 1.00 49.25     B2
ATOM  2209 C    ASP  313   44.187 27.699 21.059 1.00 35.12     B2
ATOM  2210 O    ASP  313   44.807 28.390 21.894 1.00 38.60     B2
ATOM  2211 N    PHE  314   43.192 28.216 20.339 1.00 33.36     B2
ATOM  2212 H    PHE  314   42.784 27.683 19.619 1.00  0.00     B2
ATOM  2213 CA   PHE  314   42.715 29.548 20.600 1.00 31.09     B2
ATOM  2214 CB   PHE  314   41.572 29.860 19.631 1.00 32.06     B2
ATOM  2215 CG   PHE  314   41.074 31.303 19.636 1.00 33.37     B2
ATOM  2216 CD1  PHE  314   39.780 31.568 19.247 1.00 31.81     B2
ATOM  2217 CD2  PHE  314   41.907 32.354 20.021 1.00 35.65     B2
ATOM  2218 CE1  PHE  314   39.318 32.857 19.240 1.00 29.15     B2
ATOM  2219 CE2  PHE  314   41.455 33.648 20.017 1.00 32.48     B2
ATOM  2220 CZ   PHE  314   40.154 33.870 19.622 1.00 32.81     B2
ATOM  2221 C    PHE  314   42.282 29.601 22.057 1.00 29.90     B2
ATOM  2222 O    PHE  314   42.658 30.550 22.764 1.00 26.87     B2
ATOM  2223 N    ALA  315   41.686 28.532 22.584 1.00 29.29     B2
ATOM  2224 H    ALA  315   41.448 27.764 22.022 1.00  0.00     B2
ATOM  2225 CA   ALA  315   41.300 28.583 23.961 1.00 31.61     B2
ATOM  2226 CB   ALA  315   40.632 27.358 24.451 1.00 32.23     B2
ATOM  2227 C    ALA  315   42.482 28.751 24.836 1.00 34.41     B2
ATOM  2228 O    ALA  315   42.361 29.437 25.853 1.00 37.66     B2
ATOM  2229 N    THR  316   43.646 28.250 24.476 1.00 36.16     B2
ATOM  2230 H    THR  316   43.745 27.778 23.625 1.00  0.00     B2
```

FIG.5EE

FIG.5FF

ATOM	2231	CA	THR	316	44.780	28.388	25.374	1.00	37.99	B2
ATOM	2232	CB	THR	316	45.795	27.255	25.156	1.00	41.16	B2
ATOM	2233	OG1	THR	316	45.049	26.081	25.521	1.00	45.50	B2
ATOM	2234	HG1	THR	316	44.316	25.900	24.913	1.00	0.00	B2
ATOM	2235	CG2	THR	316	47.152	27.415	25.888	1.00	40.31	B2
ATOM	2236	C	THR	316	45.458	29.710	25.177	1.00	38.47	B2
ATOM	2237	O	THR	316	45.903	30.189	26.217	1.00	39.63	B2
ATOM	2238	N	THR	317	45.620	30.287	23.970	1.00	36.53	B2
ATOM	2239	H	THR	317	45.351	29.800	23.164	1.00	0.00	B2
ATOM	2240	CA	THR	317	46.092	31.657	23.844	1.00	37.07	B2
ATOM	2241	CB	THR	317	45.866	32.098	22.392	1.00	36.01	B2
ATOM	2242	OG1	THR	317	46.752	31.352	21.575	1.00	35.31	B2
ATOM	2243	HG1	THR	317	46.489	30.441	21.389	1.00	0.00	B2
ATOM	2244	CG2	THR	317	46.109	33.566	22.156	1.00	34.30	B2
ATOM	2245	C	THR	317	45.338	32.597	24.832	1.00	39.30	B2
ATOM	2246	O	THR	317	45.941	33.378	25.583	1.00	40.17	B2
ATOM	2247	N	ILE	318	44.003	32.481	24.912	1.00	40.83	B2
ATOM	2248	H	ILE	318	43.554	31.819	24.342	1.00	0.00	B2
ATOM	2249	CA	ILE	318	43.172	33.317	25.788	1.00	40.75	B2
ATOM	2250	CB	ILE	318	41.621	32.979	25.567	1.00	37.17	B2
ATOM	2251	CG2	ILE	318	40.742	33.706	26.545	1.00	34.29	B2
ATOM	2252	CG1	ILE	318	41.216	33.310	24.160	1.00	31.39	B2
ATOM	2253	CD	ILE	318	41.626	34.657	23.614	1.00	29.66	B2
ATOM	2254	C	ILE	318	43.624	33.019	27.217	1.00	42.43	B2
ATOM	2255	O	ILE	318	44.064	33.963	27.856	1.00	42.54	B2
ATOM	2256	N	TRP	319	43.662	31.784	27.744	1.00	44.17	B2
ATOM	2257	H	TRP	319	43.537	31.008	27.163	1.00	0.00	B2
ATOM	2258	CA	TRP	319	43.994	31.633	29.142	1.00	46.90	B2
ATOM	2259	CB	TRP	319	43.892	30.179	29.597	1.00	50.64	B2
ATOM	2260	CG	TRP	319	43.998	30.094	31.131	1.00	56.05	B2
ATOM	2261	CD2	TRP	319	43.005	30.397	32.038	1.00	58.61	B2
ATOM	2262	CE2	TRP	319	43.685	30.281	33.251	1.00	60.50	B2
ATOM	2263	CE3	TRP	319	41.668	30.740	32.005	1.00	60.12	B2
ATOM	2264	CD1	TRP	319	45.188	29.788	31.760	1.00	58.07	B2
ATOM	2265	NE1	TRP	319	44.968	29.921	33.042	1.00	60.07	B2
ATOM	2266	HE1	TRP	319	45.637	29.765	33.740	1.00	0.00	B2
ATOM	2267	CZ2	TRP	319	43.044	30.512	34.456	1.00	61.00	B2
ATOM	2268	CZ3	TRP	319	41.022	30.967	33.210	1.00	61.58	B2
ATOM	2269	CH2	TRP	319	41.704	30.854	34.417	1.00	62.04	B2
ATOM	2270	C	TRP	319	45.398	32.136	29.456	1.00	47.85	B2
ATOM	2271	O	TRP	319	45.635	32.772	30.490	1.00	47.99	B2
ATOM	2272	N	GLN	320	46.339	31.915	28.550	1.00	48.63	B2
ATOM	2273	H	GLN	320	46.091	31.482	27.708	1.00	0.00	B2
ATOM	2274	CA	GLN	320	47.706	32.319	28.767	1.00	49.45	B2
ATOM	2275	CB	GLN	320	48.567	31.988	27.589	1.00	51.44	B2
ATOM	2276	CG	GLN	320	48.828	30.494	27.444	1.00	55.03	B2
ATOM	2277	CD	GLN	320	49.958	30.349	26.438	1.00	60.17	B2
ATOM	2278	OE1	GLN	320	51.116	30.465	26.834	1.00	65.26	B2
ATOM	2279	NE2	GLN	320	49.771	30.145	25.131	1.00	59.32	B2
ATOM	2280	HE21	GLN	320	48.859	30.087	24.789	1.00	0.00	B2
ATOM	2281	HE22	GLN	320	50.582	30.083	24.590	1.00	0.00	B2
ATOM	2282	C	GLN	320	47.717	33.790	28.983	1.00	49.62	B2
ATOM	2283	O	GLN	320	48.251	34.209	29.987	1.00	49.91	B2
ATOM	2284	N	GLN	321	46.998	34.538	28.150	1.00	51.76	B2
ATOM	2285	H	GLN	321	46.535	34.102	27.403	1.00	0.00	B2
ATOM	2286	CA	GLN	321	46.837	35.988	28.278	1.00	52.08	B2
ATOM	2287	CB	GLN	321	46.015	36.571	27.151	1.00	49.72	B2
ATOM	2288	CG	GLN	321	45.873	38.058	27.166	1.00	51.19	B2
ATOM	2289	CD	GLN	321	47.211	38.781	27.201	1.00	53.13	B2
ATOM	2290	OE1	GLN	321	48.090	38.622	26.364	1.00	55.36	B2
ATOM	2291	NE2	GLN	321	47.468	39.618	28.177	1.00	53.21	B2
ATOM	2292	HE21	GLN	321	46.800	39.713	28.889	1.00	0.00	B2
ATOM	2293	HE22	GLN	321	48.338	40.057	28.168	1.00	0.00	B2
ATOM	2294	C	GLN	321	46.112	36.315	29.562	1.00	53.30	B2
ATOM	2295	O	GLN	321	46.293	37.422	30.058	1.00	54.39	B2
ATOM	2296	N	MET	322	45.269	35.441	30.117	1.00	54.50	B2
ATOM	2297	H	MET	322	45.098	34.592	29.662	1.00	0.00	B2
ATOM	2298	CA	MET	322	44.619	35.748	31.375	1.00	55.42	B2
ATOM	2299	CB	MET	322	43.595	34.690	31.713	1.00	52.93	B2
ATOM	2300	CG	MET	322	42.527	34.865	30.658	1.00	51.76	B2
ATOM	2301	SD	MET	322	40.861	34.428	31.189	1.00	54.19	B2
ATOM	2302	CE	MET	322	40.293	33.192	30.069	1.00	52.53	B2

FIG.56G

```
ATOM 2303 C   MET 322  45.700 35.811 32.432 1.00 57.69 B2
ATOM 2304 O   MET 322  45.781 36.739 33.248 1.00 57.85 B2
ATOM 2305 N   GLU 323  46.652 34.900 32.319 1.00 60.28 B2
ATOM 2306 H   GLU 323  46.637 34.296 31.544 1.00  0.00 B2
ATOM 2307 CA  GLU 323  47.741 34.875 33.273 1.00 62.99 B2
ATOM 2308 CB  GLU 323  48.558 33.635 32.957 1.00 65.81 B2
ATOM 2309 CG  GLU 323  47.640 32.423 32.918 1.00 68.36 B2
ATOM 2310 CD  GLU 323  48.303 31.125 33.310 1.00 71.21 B2
ATOM 2311 OE1 GLU 323  47.651 30.364 34.044 1.00 71.19 B2
ATOM 2312 OE2 GLU 323  49.451 30.900 32.884 1.00 72.43 B2
ATOM 2313 C   GLU 323  48.648 36.124 33.418 1.00 63.96 B2
ATOM 2314 OT1 GLU 323  48.782 36.492 34.584 1.00 64.11 B2
ATOM 2315 OT2 GLU 323  49.169 36.725 32.449 1.00 62.96 B2
ATOM 2316 CB  MET 338  27.559 17.690 25.056 1.00 62.56 B3
ATOM 2317 CG  MET 338  28.087 18.862 24.222 1.00 63.85 B3
ATOM 2318 SD  MET 338  28.738 20.224 25.219 1.00 66.95 B3
ATOM 2319 CE  MET 338  27.328 21.252 25.515 1.00 65.50 B3
ATOM 2320 C   MET 338  24.988 17.301 25.122 1.00 57.55 B3
ATOM 2321 O   MET 338  24.417 16.347 25.667 1.00 56.47 B3
ATOM 2322 HT1 MET 338  26.255 16.010 26.594 1.00  0.00 B3
ATOM 2323 HT2 MET 338  25.375 17.061 27.500 1.00  0.00 B3
ATOM 2324 N   MET 338  26.286 16.971 27.009 1.00 61.55 B3
ATOM 2325 HT3 MET 338  27.108 17.107 27.620 1.00  0.00 B3
ATOM 2326 CA  MET 338  26.226 17.853 25.851 1.00 60.35 B3
ATOM 2327 N   PRO 339  24.493 17.830 23.998 1.00 55.58 B3
ATOM 2328 CD  PRO 339  24.914 19.075 23.375 1.00 54.39 B3
ATOM 2329 CA  PRO 339  23.453 17.226 23.164 1.00 54.62 B3
ATOM 2330 CB  PRO 339  23.463 18.098 21.903 1.00 53.52 B3
ATOM 2331 CG  PRO 339  24.845 18.711 21.909 1.00 53.04 B3
ATOM 2332 C   PRO 339  23.666 15.748 22.881 1.00 53.61 B3
ATOM 2333 O   PRO 339  24.730 15.222 23.169 1.00 53.35 B3
ATOM 2334 N   ALA 340  22.704 15.045 22.333 1.00 54.32 B3
ATOM 2335 H   ALA 340  21.844 15.460 22.111 1.00  0.00 B3
ATOM 2336 CA  ALA 340  22.909 13.651 21.968 1.00 56.04 B3
ATOM 2337 CB  ALA 340  21.867 12.713 22.625 1.00 57.60 B3
ATOM 2338 C   ALA 340  22.617 13.713 20.495 1.00 55.61 B3

ATOM 2339 O   ALA 340  21.426 13.783 20.196 1.00 58.64 B3
ATOM 2340 N   PHE 341  23.516 13.734 19.514 1.00 53.34 B3
ATOM 2341 H   PHE 341  24.472 13.607 19.685 1.00  0.00 B3
ATOM 2342 CA  PHE 341  23.016 13.900 18.158 1.00 49.92 B3
ATOM 2343 CB  PHE 341  24.050 14.541 17.244 1.00 48.16 B3
ATOM 2344 CG  PHE 341  24.382 15.940 17.658 1.00 45.00 B3
ATOM 2345 CD1 PHE 341  23.510 16.923 17.359 1.00 43.44 B3
ATOM 2346 CD2 PHE 341  25.527 16.175 18.388 1.00 47.03 B3
ATOM 2347 CE1 PHE 341  23.812 18.172 17.831 1.00 49.15 B3
ATOM 2348 CE2 PHE 341  25.827 17.426 18.862 1.00 47.86 B3
ATOM 2349 CZ  PHE 341  24.952 18.437 18.580 1.00 48.36 B3
ATOM 2350 C   PHE 341  22.684 12.510 17.672 1.00 49.56 B3
ATOM 2351 O   PHE 341  23.309 11.938 16.781 1.00 51.46 B3
ATOM 2352 N   ALA 342  21.625 11.985 18.245 1.00 47.40 B3
ATOM 2353 H   ALA 342  21.026 12.585 18.741 1.00  0.00 B3
ATOM 2354 CA  ALA 342  21.167 10.650 17.997 1.00 46.11 B3
ATOM 2355 CB  ALA 342  19.874 10.531 18.804 1.00 47.10 B3
ATOM 2356 C   ALA 342  20.962 10.149 16.556 1.00 44.37 B3
ATOM 2357 O   ALA 342  20.138  9.247 16.418 1.00 45.65 B3
ATOM 2358 N   SER 343  21.537 10.573 15.423 1.00 41.37 B3
ATOM 2359 H   SER 343  22.191 11.301 15.428 1.00  0.00 B3
ATOM 2360 CA  SER 343  21.274  9.923 14.145 1.00 38.80 B3
ATOM 2361 CB  SER 343  19.842 10.138 13.656 1.00 38.79 B3
ATOM 2362 OG  SER 343  19.205 11.300 14.182 1.00 37.75 B3
ATOM 2363 HG  SER 343  18.963 11.059 15.092 1.00  0.00 B3
ATOM 2364 C   SER 343  22.172 10.467 13.088 1.00 38.22 B3
ATOM 2365 O   SER 343  22.810 11.471 13.382 1.00 38.30 B3
ATOM 2366 N   ALA 344  22.206  9.845 11.888 1.00 36.73 B3
ATOM 2367 H   ALA 344  21.762  8.978 11.805 1.00  0.00 B3
ATOM 2368 CA  ALA 344  22.914 10.384 10.715 1.00 38.09 B3
ATOM 2369 CB  ALA 344  22.583  9.640  9.422 1.00 36.78 B3
ATOM 2370 C   ALA 344  22.477 11.842 10.496 1.00 37.72 B3
ATOM 2371 O   ALA 344  23.271 12.765 10.676 1.00 38.42 B3
ATOM 2372 N   PHE 345  21.194 12.042 10.163 1.00 36.10 B3
ATOM 2373 H   PHE 345  20.668 11.298  9.811 1.00  0.00 B3
ATOM 2374 CA  PHE 345  20.564 13.338 10.195 1.00 34.69 B3
```

FIG.5HH

```
ATOM 2375 CB  PHE 345  19.040 13.254 10.128 1.00 33.24 B3
ATOM 2376 CG  PHE 345  18.462 14.656  9.918 1.00 31.72 B3
ATOM 2377 CD1 PHE 345  17.715 15.223 10.905 1.00 26.64 B3
ATOM 2378 CD2 PHE 345  18.767 15.343  8.745 1.00 29.99 B3
ATOM 2379 CE1 PHE 345  17.284 16.503 10.682 1.00 33.56 B3
ATOM 2380 CE2 PHE 345  18.333 16.619  8.537 1.00 30.81 B3
ATOM 2381 CZ  PHE 345  17.581 17.201  9.520 1.00 31.44 B3
ATOM 2382 C   PHE 345  20.888 14.145 11.458 1.00 35.02 B3
ATOM 2383 O   PHE 345  21.246 15.319 11.292 1.00 37.81 B3
ATOM 2384 N   GLN 346  20.814 13.688 12.691 1.00 32.53 B3
ATOM 2385 H   GLN 346  20.516 12.778 12.894 1.00  0.00 B3
ATOM 2386 CA  GLN 346  21.156 14.586 13.758 1.00 33.46 B3
ATOM 2387 CB  GLN 346  20.899 13.985 15.061 1.00 33.80 B3
ATOM 2388 CG  GLN 346  19.459 14.284 15.174 1.00 35.68 B3
ATOM 2389 CD  GLN 346  18.788 13.658 16.344 1.00 38.48 B3
ATOM 2390 OE1 GLN 346  19.358 13.328 17.374 1.00 41.78 B3
ATOM 2391 NE2 GLN 346  17.508 13.463 16.167 1.00 41.08 B3
ATOM 2392 HE21 GLN 346 17.088 13.724 15.323 1.00  0.00 B3
ATOM 2393 HE22 GLN 346 17.026 13.063 16.919 1.00  0.00 B3
ATOM 2394 C   GLN 346  22.564 15.051 13.773 1.00 35.73 B3
ATOM 2395 O   GLN 346  22.766 16.231 14.051 1.00 38.18 B3
ATOM 2396 N   ARG 347  23.507 14.190 13.431 1.00 35.57 B3
ATOM 2397 H   ARG 347  23.248 13.289 13.157 1.00  0.00 B3
ATOM 2398 CA  ARG 347  24.907 14.538 13.396 1.00 35.95 B3
ATOM 2399 CB  ARG 347  25.760 13.236 13.222 1.00 36.20 B3
ATOM 2400 CG  ARG 347  26.198 12.549 14.540 1.00 37.41 B3
ATOM 2401 CD  ARG 347  26.986 11.246 14.373 1.00 39.70 B3
ATOM 2402 NE  ARG 347  26.072 10.167 14.028 1.00 47.18 B3
ATOM 2403 HE  ARG 347  25.416  9.893 14.701 1.00  0.00 B3
ATOM 2404 CZ  ARG 347  26.071  9.516 12.846 1.00 48.49 B3
ATOM 2405 NH1 ARG 347  26.938  9.802 11.882 1.00 50.22 B3
ATOM 2406 HH11 ARG 347 27.602 10.528 12.031 1.00  0.00 B3
ATOM 2407 HH12 ARG 347 26.905  9.313 11.011 1.00  0.00 B3
ATOM 2408 NH2 ARG 347  25.130  8.608 12.574 1.00 48.46 B3
ATOM 2409 HH21 ARG 347 24.423  8.408 13.252 1.00  0.00 B3
ATOM 2410 HH22 ARG 347 25.126  8.131 11.697 1.00  0.00 B3
ATOM 2411 C   ARG 347  25.183 15.544 12.267 1.00 35.54 B3
ATOM 2412 O   ARG 347  25.877 16.549 12.445 1.00 36.73 B3
ATOM 2413 N   ARG 348  24.611 15.353 11.096 1.00 34.74 B3
ATOM 2414 H   ARG 348  24.043 14.559 11.005 1.00  0.00 B3
ATOM 2415 CA  ARG 348  24.802 16.225  9.954 1.00 35.24 B3
ATOM 2416 CB  ARG 348  24.091 15.623  8.751 1.00 36.76 B3
ATOM 2417 CG  ARG 348  24.778 14.303  8.450 1.00 44.22 B3
ATOM 2418 CD  ARG 348  24.014 13.379  7.529 1.00 49.23 B3
ATOM 2419 NE  ARG 348  24.705 12.090  7.457 1.00 54.27 B3
ATOM 2420 HE  ARG 348  25.300 11.836  8.193 1.00  0.00 B3
ATOM 2421 CZ  ARG 348  24.557 11.226  6.430 1.00 53.75 B3
ATOM 2422 NH1 ARG 348  23.758 11.479  5.381 1.00 51.85 B3
ATOM 2423 HH11 ARG 348 23.234 12.329  5.339 1.00  0.00 B3
ATOM 2424 HH12 ARG 348 23.680 10.807  4.645 1.00  0.00 B3
ATOM 2425 NH2 ARG 348  25.252 10.083  6.462 1.00 54.51 B3
ATOM 2426 HH21 ARG 348 25.169  9.424  5.714 1.00  0.00 B3
ATOM 2427 HH22 ARG 348 25.860  9.894  7.232 1.00  0.00 B3
ATOM 2428 C   ARG 348  24.283 17.629 10.237 1.00 34.80 B3
ATOM 2429 O   ARG 348  25.078 18.564 10.219 1.00 35.16 B3
ATOM 2430 N   ALA 349  23.008 17.795 10.607 1.00 33.85 B3
ATOM 2431 H   ALA 349  22.470 16.984 10.755 1.00  0.00 B3
ATOM 2432 CA  ALA 349  22.352 19.083 10.853 1.00 32.96 B3
ATOM 2433 CB  ALA 349  20.809 18.894 11.070 1.00 33.36 B3
ATOM 2434 C   ALA 349  22.945 19.746 12.083 1.00 31.84 B3
ATOM 2435 O   ALA 349  22.981 20.969 12.210 1.00 30.69 B3
ATOM 2436 N   GLY 350  23.444 18.954 13.018 1.00 31.30 B3
ATOM 2437 H   GLY 350  23.308 17.984 12.976 1.00  0.00 B3
ATOM 2438 CA  GLY 350  24.117 19.505 14.181 1.00 31.08 B3
ATOM 2439 C   GLY 350  25.462 20.025 13.753 1.00 30.79 B3
ATOM 2440 O   GLY 350  25.974 21.010 14.280 1.00 31.38 B3
ATOM 2441 N   GLY 351  25.991 19.374 12.731 1.00 30.03 B3
ATOM 2442 H   GLY 351  25.546 18.582 12.367 1.00  0.00 B3
ATOM 2443 CA  GLY 351  27.263 19.735 12.184 1.00 29.95 B3
ATOM 2444 C   GLY 351  27.182 21.097 11.534 1.00 29.25 B3
ATOM 2445 O   GLY 351  27.937 21.974 11.919 1.00 28.73 B3
ATOM 2446 N   VAL 352  26.336 21.285 10.522 1.00 28.92 B3
```

FIG.5IJ

ATOM	2447	H	VAL	352	25.859	20.484	10.214	1.00	0.00	B3
ATOM	2448	CA	VAL	352	26.079	22.567	9.881	1.00	28.59	B3
ATOM	2449	CB	VAL	352	24.845	22.452	9.004	1.00	28.96	B3
ATOM	2450	CG1	VAL	352	24.627	23.785	8.346	1.00	30.86	B3
ATOM	2451	CG2	VAL	352	25.021	21.475	7.875	1.00	26.94	B3
ATOM	2452	C	VAL	352	25.849	23.709	10.890	1.00	29.29	B3
ATOM	2453	O	VAL	352	26.520	24.747	10.853	1.00	31.02	B3
ATOM	2454	N	LEU	353	24.923	23.543	11.819	1.00	27.52	B3
ATOM	2455	H	LEU	353	24.404	22.709	11.838	1.00	0.00	B3
ATOM	2456	CA	LEU	353	24.635	24.548	12.817	1.00	26.18	B3
ATOM	2457	CB	LEU	353	23.434	24.113	13.636	1.00	27.87	B3
ATOM	2458	CG	LEU	353	22.098	24.034	12.931	1.00	26.54	B3
ATOM	2459	CD1	LEU	353	21.064	23.617	13.924	1.00	25.49	B3
ATOM	2460	CD2	LEU	353	21.750	25.372	12.320	1.00	28.23	B3
ATOM	2461	C	LEU	353	25.742	24.905	13.772	1.00	27.17	B3
ATOM	2462	O	LEU	353	25.838	26.093	14.088	1.00	28.00	B3
ATOM	2463	N	VAL	354	26.539	23.949	14.318	1.00	27.20	B3
ATOM	2464	H	VAL	354	26.321	23.006	14.139	1.00	0.00	B3
ATOM	2465	CA	VAL	354	27.712	24.212	15.157	1.00	24.62	B3
ATOM	2466	CB	VAL	354	28.236	22.910	15.745	1.00	22.01	B3
ATOM	2467	CG1	VAL	354	29.568	23.089	16.406	1.00	19.82	B3
ATOM	2468	CG2	VAL	354	27.276	22.467	16.802	1.00	23.96	B3
ATOM	2469	C	VAL	354	28.812	24.893	14.332	1.00	25.46	B3
ATOM	2470	O	VAL	354	29.439	25.832	14.798	1.00	26.23	B3
ATOM	2471	N	ALA	355	29.059	24.530	13.089	1.00	26.12	B3
ATOM	2472	H	ALA	355	28.579	23.745	12.744	1.00	0.00	B3
ATOM	2473	CA	ALA	355	30.025	25.180	12.235	1.00	26.54	B3
ATOM	2474	CB	ALA	355	30.034	24.591	10.869	1.00	22.08	B3
ATOM	2475	C	ALA	355	29.533	26.601	12.096	1.00	28.51	B3
ATOM	2476	O	ALA	355	30.315	27.498	12.344	1.00	31.93	B3
ATOM	2477	N	SER	356	28.271	26.884	11.802	1.00	30.30	B3
ATOM	2478	H	SER	356	27.654	26.134	11.665	1.00	0.00	B3
ATOM	2479	CA	SER	356	27.778	28.249	11.625	1.00	31.10	B3
ATOM	2480	CB	SER	356	26.401	28.147	11.016	1.00	35.23	B3
ATOM	2481	OG	SER	356	25.679	29.380	10.905	1.00	43.82	B3
ATOM	2482	HG	SER	356	26.250	30.004	10.429	1.00	0.00	B3
ATOM	2483	C	SER	356	27.763	29.095	12.901	1.00	29.75	B3
ATOM	2484	O	SER	356	28.115	30.289	12.898	1.00	28.35	B3
ATOM	2485	N	HIS	357	27.465	28.464	14.025	1.00	27.82	B3
ATOM	2486	H	HIS	357	27.301	27.498	14.019	1.00	0.00	B3
ATOM	2487	CA	HIS	357	27.434	29.194	15.259	1.00	26.58	B3
ATOM	2488	CB	HIS	357	26.735	28.365	16.305	1.00	25.77	B3
ATOM	2489	CG	HIS	357	25.219	28.360	16.063	1.00	27.67	B3
ATOM	2490	CD2	HIS	357	24.563	28.767	14.915	1.00	28.94	B3
ATOM	2491	ND1	HIS	357	24.277	27.963	16.915	1.00	28.43	B3
ATOM	2492	HD1	HIS	357	24.456	27.622	17.828	1.00	0.00	B3
ATOM	2493	CE1	HIS	357	23.112	28.103	16.337	1.00	28.64	B3
ATOM	2494	NE2	HIS	357	23.298	28.589	15.130	1.00	29.48	B3
ATOM	2495	HE2	HIS	357	22.576	28.801	14.495	1.00	0.00	B3
ATOM	2496	C	HIS	357	28.852	29.506	15.645	1.00	27.93	B3
ATOM	2497	O	HIS	357	29.119	30.606	16.115	1.00	29.15	B3
ATOM	2498	N	LEU	358	29.830	28.637	15.383	1.00	28.33	B3
ATOM	2499	H	LEU	358	29.624	27.761	14.997	1.00	0.00	B3
ATOM	2500	CA	LEU	358	31.211	28.940	15.721	1.00	26.39	B3
ATOM	2501	CB	LEU	358	32.030	27.702	15.547	1.00	21.42	B3
ATOM	2502	CG	LEU	358	33.457	27.878	15.734	1.00	20.42	B3
ATOM	2503	CD1	LEU	358	33.805	28.078	17.165	1.00	16.79	B3
ATOM	2504	CD2	LEU	358	34.075	26.714	15.072	1.00	22.89	B3
ATOM	2505	C	LEU	358	31.721	30.067	14.822	1.00	26.45	B3
ATOM	2506	O	LEU	358	32.372	30.939	15.378	1.00	27.12	B3
ATOM	2507	N	GLN	359	31.460	30.130	13.518	1.00	26.41	B3
ATOM	2508	H	GLN	359	31.048	29.337	13.114	1.00	0.00	B3
ATOM	2509	CA	GLN	359	31.863	31.254	12.671	1.00	29.10	B3
ATOM	2510	CB	GLN	359	31.204	31.209	11.292	1.00	30.49	B3
ATOM	2511	CG	GLN	359	31.395	29.952	10.455	1.00	38.94	B3
ATOM	2512	CD	GLN	359	32.842	29.636	10.091	1.00	42.09	B3
ATOM	2513	OE1	GLN	359	33.774	29.979	10.821	1.00	46.15	B3
ATOM	2514	NE2	GLN	359	33.103	28.987	8.967	1.00	41.34	B3
ATOM	2515	HE21	GLN	359	32.341	28.706	8.412	1.00	0.00	B3
ATOM	2516	HE22	GLN	359	34.039	28.838	8.740	1.00	0.00	B3
ATOM	2517	C	GLN	359	31.512	32.621	13.254	1.00	29.39	B3
ATOM	2518	O	GLN	359	32.427	33.427	13.484	1.00	30.06	B3

FIG.5JJ

```
ATOM 2519 N   SER 360 30.201 32.810 13.528 1.00 28.66 B3
ATOM 2520 H   SER 360 29.595 32.061 13.343 1.00  0.00 B3
ATOM 2521 CA  SER 360 29.570 34.003 14.071 1.00 27.31 B3
ATOM 2522 CB  SER 360 28.121 33.761 14.336 1.00 26.70 B3
ATOM 2523 OG  SER 360 27.493 33.539 13.078 1.00 29.72 B3
ATOM 2524 HG  SER 360 26.637 33.112 13.288 1.00  0.00 B3
ATOM 2525 C   SER 360 30.202 34.387 15.353 1.00 27.15 B3
ATOM 2526 O   SER 360 30.575 35.550 15.498 1.00 26.93 B3
ATOM 2527 N   PHE 361 30.383 33.403 16.246 1.00 25.38 B3
ATOM 2528 H   PHE 361 30.055 32.499 16.040 1.00  0.00 B3
ATOM 2529 CA  PHE 361 31.066 33.626 17.517 1.00 25.20 B3
ATOM 2530 CB  PHE 361 31.092 32.335 18.302 1.00 23.30 B3
ATOM 2531 CG  PHE 361 31.796 32.394 19.655 1.00 23.63 B3
ATOM 2532 CD1 PHE 361 31.127 32.854 20.777 1.00 22.44 B3
ATOM 2533 CD2 PHE 361 33.098 31.931 19.770 1.00 23.35 B3
ATOM 2534 CE1 PHE 361 31.772 32.834 22.000 1.00 22.78 B3
ATOM 2535 CE2 PHE 361 33.719 31.921 21.002 1.00 21.26 B3
ATOM 2536 CZ  PHE 361 33.058 32.368 22.114 1.00 19.54 B3
ATOM 2537 C   PHE 361 32.505 34.143 17.385 1.00 26.56 B3
ATOM 2538 O   PHE 361 32.914 34.979 18.183 1.00 26.76 B3
ATOM 2539 N   LEU 362 33.309 33.645 16.441 1.00 28.17 B3
ATOM 2540 H   LEU 362 32.962 32.921 15.874 1.00  0.00 B3
ATOM 2541 CA  LEU 362 34.679 34.089 16.222 1.00 28.89 B3
ATOM 2542 CB  LEU 362 35.452 33.125 15.338 1.00 28.18 B3
ATOM 2543 CG  LEU 362 35.603 31.656 15.781 1.00 29.61 B3
ATOM 2544 CD1 LEU 362 36.306 30.996 14.633 1.00 31.63 B3
ATOM 2545 CD2 LEU 362 36.374 31.433 17.055 1.00 26.38 B3
ATOM 2546 C   LEU 362 34.692 35.449 15.536 1.00 29.18 B3
ATOM 2547 O   LEU 362 35.649 36.202 15.748 1.00 27.43 B3
ATOM 2548 N   GLU 363 33.664 35.763 14.710 1.00 29.54 B3
ATOM 2549 H   GLU 363 33.009 35.066 14.495 1.00  0.00 B3
ATOM 2550 CA  GLU 363 33.496 37.090 14.145 1.00 30.30 B3
ATOM 2551 CB  GLU 363 32.357 37.147 13.228 1.00 30.90 B3
ATOM 2552 CG  GLU 363 32.763 36.735 11.849 1.00 38.69 B3
ATOM 2553 CD  GLU 363 33.642 37.662 11.013 1.00 42.62 B3
ATOM 2554 OE1 GLU 363 33.896 37.282  9.860 1.00 46.58 B3
ATOM 2555 OE2 GLU 363 34.051 38.734 11.488 1.00 46.47 B3
ATOM 2556 C   GLU 363 33.229 38.098 15.244 1.00 30.19 B3
ATOM 2557 O   GLU 363 33.837 39.167 15.239 1.00 30.26 B3
ATOM 2558 N   VAL 364 32.397 37.726 16.217 1.00 30.04 B3
ATOM 2559 H   VAL 364 31.888 36.898 16.100 1.00  0.00 B3
ATOM 2560 CA  VAL 364 32.178 38.522 17.400 1.00 31.90 B3
ATOM 2561 CB  VAL 364 31.014 38.021 18.269 1.00 31.41 B3
ATOM 2562 CG1 VAL 364 30.860 38.811 19.562 1.00 30.73 B3
ATOM 2563 CG2 VAL 364 29.750 38.200 17.497 1.00 29.96 B3
ATOM 2564 C   VAL 364 33.402 38.493 18.275 1.00 35.89 B3
ATOM 2565 O   VAL 364 33.683 39.535 18.855 1.00 37.54 B3
ATOM 2566 N   SER 365 34.173 37.421 18.477 1.00 38.25 B3
ATOM 2567 H   SER 365 33.971 36.577 18.030 1.00  0.00 B3
ATOM 2568 CA  SER 365 35.337 37.478 19.375 1.00 39.61 B3
ATOM 2569 CB  SER 365 36.041 36.113 19.555 1.00 43.00 B3
ATOM 2570 OG  SER 365 35.201 34.953 19.575 1.00 46.29 B3
ATOM 2571 HG  SER 365 34.270 35.189 19.644 1.00  0.00 B3
ATOM 2572 C   SER 365 36.398 38.418 18.840 1.00 38.21 B3
ATOM 2573 O   SER 365 37.103 38.989 19.662 1.00 36.91 B3
ATOM 2574 N   TYR 366 36.575 38.540 17.514 1.00 38.00 B3
ATOM 2575 H   TYR 366 36.079 37.945 16.910 1.00  0.00 B3
ATOM 2576 CA  TYR 366 37.568 39.463 16.969 1.00 39.85 B3
ATOM 2577 CB  TYR 366 37.776 39.330 15.436 1.00 38.53 B3
ATOM 2578 CG  TYR 366 38.662 40.447 14.879 1.00 38.21 B3
ATOM 2579 CD1 TYR 366 38.104 41.464 14.129 1.00 37.18 B3
ATOM 2580 CE1 TYR 366 38.918 42.495 13.678 1.00 41.77 B3
ATOM 2581 CD2 TYR 366 40.021 40.443 15.182 1.00 40.21 B3
ATOM 2582 CE2 TYR 366 40.849 41.466 14.739 1.00 40.76 B3
ATOM 2583 CZ  TYR 366 40.297 42.504 13.976 1.00 42.82 B3
ATOM 2584 OH  TYR 366 41.151 43.522 13.493 1.00 41.30 B3
ATOM 2585 HH  TYR 366 40.743 43.977 12.755 1.00  0.00 B3
ATOM 2586 C   TYR 366 37.133 40.893 17.241 1.00 40.55 B3
ATOM 2587 O   TYR 366 37.917 41.647 17.798 1.00 40.92 B3
ATOM 2588 N   ARG 367 35.933 41.309 16.853 1.00 41.88 B3
ATOM 2589 H   ARG 367 35.360 40.682 16.360 1.00  0.00 B3
ATOM 2590 CA  ARG 367 35.442 42.653 17.139 1.00 43.32 B3
```

FIG.5KK

ATOM	2591	CB	ARG	367	34.013	42.709	16.650	1.00	46.82	B3
ATOM	2592	CG	ARG	367	33.528	44.130	16.650	1.00	56.74	B3
ATOM	2593	CD	ARG	367	32.069	44.267	16.248	1.00	61.81	B3
ATOM	2594	NE	ARG	367	31.723	45.687	16.229	1.00	66.59	B3
ATOM	2595	HE	ARG	367	32.438	46.356	16.172	1.00	0.00	B3
ATOM	2596	CZ	ARG	367	30.458	46.091	16.308	1.00	69.75	B3
ATOM	2597	NH1	ARG	367	29.448	45.220	16.413	1.00	72.65	B3
ATOM	2598	HH11	ARG	367	29.631	44.236	16.410	1.00	0.00	B3
ATOM	2599	HH12	ARG	367	28.503	45.548	16.445	1.00	0.00	B3
ATOM	2600	NH2	ARG	367	30.160	47.375	16.162	1.00	71.64	B3
ATOM	2601	HH21	ARG	367	29.204	47.665	16.222	1.00	0.00	B3
ATOM	2602	HH22	ARG	367	30.888	48.043	16.013	1.00	0.00	B3
ATOM	2603	C	ARG	367	35.551	43.011	18.635	1.00	40.96	B3
ATOM	2604	O	ARG	367	35.994	44.090	19.012	1.00	41.10	B3
ATOM	2605	N	VAL	368	35.160	42.135	19.542	1.00	39.83	B3
ATOM	2606	H	VAL	368	34.726	41.316	19.217	1.00	0.00	B3
ATOM	2607	CA	VAL	368	35.331	42.292	20.968	1.00	37.33	B3
ATOM	2608	CB	VAL	368	34.748	41.043	21.664	1.00	35.75	B3
ATOM	2609	CG1	VAL	368	35.087	40.867	23.140	1.00	35.10	B3
ATOM	2610	CG2	VAL	368	33.259	41.230	21.586	1.00	33.28	B3
ATOM	2611	C	VAL	368	36.813	42.459	21.223	1.00	38.75	B3
ATOM	2612	O	VAL	368	37.144	43.498	21.772	1.00	40.11	B3
ATOM	2613	N	LEU	369	37.759	41.600	20.835	1.00	39.59	B3
ATOM	2614	H	LEU	369	37.492	40.818	20.308	1.00	0.00	B3
ATOM	2615	CA	LEU	369	39.180	41.780	21.148	1.00	40.05	B3
ATOM	2616	CB	LEU	369	39.984	40.601	20.679	1.00	37.15	B3
ATOM	2617	CG	LEU	369	39.831	39.335	21.426	1.00	37.54	B3
ATOM	2618	CD1	LEU	369	40.349	38.238	20.528	1.00	39.70	B3
ATOM	2619	CD2	LEU	369	40.563	39.394	22.747	1.00	36.86	B3
ATOM	2620	C	LEU	369	39.817	43.031	20.542	1.00	41.88	B3
ATOM	2621	O	LEU	369	40.711	43.654	21.144	1.00	41.30	B3
ATOM	2622	N	ARG	370	39.333	43.413	19.354	1.00	42.80	B3
ATOM	2623	H	ARG	370	38.619	42.884	18.957	1.00	0.00	B3
ATOM	2624	CA	ARG	370	39.819	44.577	18.663	1.00	44.96	B3
ATOM	2625	CB	ARG	370	39.184	44.569	17.316	1.00	42.06	B3
ATOM	2626	CG	ARG	370	39.424	45.719	16.371	1.00	43.93	B3
ATOM	2627	CD	ARG	370	40.894	45.910	16.169	1.00	45.37	B3
ATOM	2628	NE	ARG	370	41.219	46.681	14.976	1.00	48.00	B3
ATOM	2629	HE	ARG	370	40.524	46.867	14.312	1.00	0.00	B3
ATOM	2630	CZ	ARG	370	42.469	47.153	14.791	1.00	48.45	B3
ATOM	2631	NH1	ARG	370	43.443	46.961	15.691	1.00	49.13	B3
ATOM	2632	HH11	ARG	370	43.262	46.456	16.534	1.00	0.00	B3
ATOM	2633	HH12	ARG	370	44.357	47.326	15.520	1.00	0.00	B3
ATOM	2634	NH2	ARG	370	42.821	47.710	13.635	1.00	47.59	B3
ATOM	2635	HH21	ARG	370	42.163	47.785	12.889	1.00	0.00	B3
ATOM	2636	HH22	ARG	370	43.751	48.057	13.516	1.00	0.00	B3
ATOM	2637	C	ARG	370	39.386	45.740	19.558	1.00	49.12	B3
ATOM	2638	O	ARG	370	40.216	46.615	19.826	1.00	49.67	B3
ATOM	2639	N	HIS	371	38.162	45.728	20.123	1.00	52.30	B3
ATOM	2640	H	HIS	371	37.581	44.955	19.949	1.00	0.00	B3
ATOM	2641	CA	HIS	371	37.745	46.738	21.080	1.00	56.65	B3
ATOM	2642	CB	HIS	371	36.284	46.604	21.459	1.00	62.15	B3
ATOM	2643	CG	HIS	371	35.320	46.991	20.346	1.00	71.70	B3
ATOM	2644	CD2	HIS	371	35.596	47.877	19.313	1.00	75.03	B3
ATOM	2645	ND1	HIS	371	34.067	46.546	20.166	1.00	75.91	B3
ATOM	2646	HD1	HIS	371	33.594	45.897	20.732	1.00	0.00	B3
ATOM	2647	CE1	HIS	371	33.580	47.116	19.077	1.00	77.30	B3
ATOM	2648	NE2	HIS	371	34.507	47.914	18.573	1.00	77.52	B3
ATOM	2649	HE2	HIS	371	34.401	48.460	17.764	1.00	0.00	B3
ATOM	2650	C	HIS	371	38.533	46.669	22.382	1.00	56.97	B3
ATOM	2651	O	HIS	371	38.458	47.592	23.176	1.00	58.12	B3
ATOM	2652	N	LEU	372	39.271	45.632	22.715	1.00	56.98	B3
ATOM	2653	H	LEU	372	39.302	44.855	22.122	1.00	0.00	B3
ATOM	2654	CA	LEU	372	40.048	45.597	23.939	1.00	57.77	B3
ATOM	2655	CB	LEU	372	39.725	44.272	24.633	1.00	57.29	B3
ATOM	2656	CG	LEU	372	38.566	44.144	25.611	1.00	55.87	B3
ATOM	2657	CD1	LEU	372	37.358	44.892	25.123	1.00	55.77	B3
ATOM	2658	CD2	LEU	372	38.211	42.675	25.749	1.00	55.33	B3
ATOM	2659	C	LEU	372	41.554	45.755	23.647	1.00	58.81	B3
ATOM	2660	O	LEU	372	42.447	45.475	24.476	1.00	59.12	B3
ATOM	2661	N	ALA	373	41.942	46.168	22.447	1.00	59.27	B3
ATOM	2662	H	ALA	373	41.271	46.255	21.731	1.00	0.00	B3

FIG.5LL

ATOM	2663	CA	ALA	373	43.336	46.425	22.147	1.00 60.03	B3
ATOM	2664	CB	ALA	373	43.755	45.485	21.021	1.00 59.87	B3
ATOM	2665	C	ALA	373	43.616	47.895	21.762	1.00 61.22	B3
ATOM	2666	OT1	ALA	373	44.798	48.243	21.697	1.00 62.45	B3
ATOM	2667	OT2	ALA	373	42.682	48.700	21.583	1.00 61.55	B3
ATOM	2668	CB	LEU	410	23.866	49.243	1.118	1.00 53.10	CI
ATOM	2669	CG	LEU	410	23.982	47.812	0.738	1.00 51.85	CI
ATOM	2670	CD1	LEU	410	25.074	47.596	-0.330	1.00 52.64	CI
ATOM	2671	CD2	LEU	410	24.125	47.081	2.058	1.00 49.28	CI
ATOM	2672	C	LEU	410	22.381	51.214	1.635	1.00 52.99	CI
ATOM	2673	O	LEU	410	22.242	52.166	0.845	1.00 53.00	CI
ATOM	2674	HT1	LEU	410	22.721	50.836	-0.665	1.00 0.00	CI
ATOM	2675	HT2	LEU	410	21.194	50.178	-0.557	1.00 0.00	CI
ATOM	2676	N	LEU	410	22.198	49.968	-0.415	1.00 54.31	CI
ATOM	2677	HT3	LEU	410	22.529	49.174	-0.998	1.00 0.00	CI
ATOM	2678	CA	LEU	410	22.478	49.815	1.004	1.00 53.64	CI
ATOM	2679	N	PRO	411	22.450	51.433	2.965	1.00 52.95	CI
ATOM	2680	CD	PRO	411	22.466	50.407	4.022	1.00 52.54	CI
ATOM	2681	CA	PRO	411	22.666	52.766	3.548	1.00 53.25	CI
ATOM	2682	CB	PRO	411	22.688	52.541	5.068	1.00 52.85	CI
ATOM	2683	CG	PRO	411	23.163	51.108	5.203	1.00 52.83	CI
ATOM	2684	C	PRO	411	23.958	53.413	3.023	1.00 53.47	CI
ATOM	2685	O	PRO	411	25.073	52.878	3.167	1.00 54.02	CI
ATOM	2686	N	GLN	412	23.787	54.599	2.411	1.00 52.79	CI
ATOM	2687	H	GLN	412	22.863	54.900	2.294	1.00 0.00	CI
ATOM	2688	CA	GLN	412	24.873	55.413	1.871	1.00 50.44	CI
ATOM	2689	CB	GLN	412	24.387	56.762	1.413	1.00 52.47	CI
ATOM	2690	CG	GLN	412	25.364	57.408	0.437	1.00 56.51	CI
ATOM	2691	CD	GLN	412	25.228	56.954	-1.017	1.00 59.40	CI
ATOM	2692	OE1	GLN	412	25.869	57.506	-1.913	1.00 59.67	CI
ATOM	2693	NE2	GLN	412	24.336	56.022	-1.389	1.00 60.12	CI
ATOM	2694	HE21	GLN	412	23.734	55.616	-0.737	1.00 0.00	CI
ATOM	2695	HE22	GLN	412	24.396	55.748	-2.328	1.00 0.00	CI
ATOM	2696	C	GLN	412	25.930	55.646	2.916	1.00 48.22	CI
ATOM	2697	O	GLN	412	27.089	55.591	2.545	1.00 46.78	CI
ATOM	2698	N	SER	413	25.614	55.842	4.201	1.00 47.90	CI
ATOM	2699	H	SER	413	24.693	55.976	4.492	1.00 0.00	CI
ATOM	2700	CA	SER	413	26.696	55.984	5.144	1.00 48.75	CI
ATOM	2701	CB	SER	413	26.261	56.344	6.548	1.00 50.61	CI
ATOM	2702	OG	SER	413	27.378	56.872	7.301	1.00 53.05	CI
ATOM	2703	HG	SER	413	28.178	56.355	7.145	1.00 0.00	CI
ATOM	2704	C	SER	413	27.480	54.684	5.267	1.00 48.71	CI
ATOM	2705	O	SER	413	28.698	54.839	5.392	1.00 50.77	CI
ATOM	2706	N	PHE	414	26.947	53.440	5.208	1.00 46.01	CI
ATOM	2707	H	PHE	414	25.996	53.323	5.015	1.00 0.00	CI
ATOM	2708	CA	PHE	414	27.787	52.233	5.274	1.00 42.92	CI
ATOM	2709	CB	PHE	414	26.959	50.915	5.232	1.00 40.76	CI
ATOM	2710	CG	PHE	414	27.633	49.627	4.757	1.00 35.06	CI
ATOM	2711	CD1	PHE	414	27.583	49.256	3.425	1.00 34.71	CI
ATOM	2712	CD2	PHE	414	28.262	48.800	5.663	1.00 34.81	CI
ATOM	2713	CE1	PHE	414	28.156	48.056	3.014	1.00 36.16	CI
ATOM	2714	CE2	PHE	414	28.832	47.602	5.247	1.00 33.40	CI
ATOM	2715	CZ	PHE	414	28.781	47.223	3.923	1.00 34.22	CI
ATOM	2716	C	PHE	414	28.667	52.271	4.044	1.00 41.25	CI
ATOM	2717	O	PHE	414	29.831	51.902	4.110	1.00 41.47	CI
ATOM	2718	N	LEU	415	28.122	52.748	2.942	1.00 39.50	CI
ATOM	2719	H	LEU	415	27.188	53.044	2.946	1.00 0.00	CI
ATOM	2720	CA	LEU	415	28.865	52.769	1.721	1.00 39.91	CI
ATOM	2721	CB	LEU	415	27.946	53.205	0.641	1.00 41.98	CI
ATOM	2722	CG	LEU	415	27.903	52.274	-0.526	1.00 44.75	CI
ATOM	2723	CD1	LEU	415	26.430	51.951	-0.780	1.00 42.93	CI
ATOM	2724	CD2	LEU	415	28.793	52.853	-1.648	1.00 45.91	CI
ATOM	2725	C	LEU	415	30.081	53.669	1.755	1.00 40.03	CI
ATOM	2726	O	LEU	415	31.142	53.348	1.183	1.00 40.28	CI
ATOM	2727	N	LEU	416	29.901	54.779	2.487	1.00 37.46	CI
ATOM	2728	H	LEU	416	29.028	54.948	2.899	1.00 0.00	CI
ATOM	2729	CA	LEU	416	30.942	55.756	2.602	1.00 34.05	CI
ATOM	2730	CB	LEU	416	30.294	57.089	2.998	1.00 34.67	CI
ATOM	2731	CG	LEU	416	29.438	57.704	1.851	1.00 35.24	CI
ATOM	2732	CD1	LEU	416	28.770	58.948	2.358	1.00 31.87	CI
ATOM	2733	CD2	LEU	416	30.310	57.948	0.593	1.00 35.50	CI
ATOM	2734	C	LEU	416	31.952	55.258	3.586	1.00 31.97	CI

FIG.5MM

```
ATOM 2735 O   LEU 416  33.131 55.427  3.270 1.00 33.32 CI
ATOM 2736 N   ALA 417  31.573 54.619  4.695 1.00 29.05 CI
ATOM 2737 H   ALA 417  30.621 54.616  4.927 1.00  0.00
ATOM 2738 CA  ALA 417  32.524 53.882  5.561 1.00 29.64 CI
ATOM 2739 CB  ALA 417  31.853 53.087  6.680 1.00 25.16 CI
ATOM 2740 C   ALA 417  33.319 52.827  4.777 1.00 30.68 CI
ATOM 2741 O   ALA 417  34.536 52.721  4.877 1.00 31.52 CI
ATOM 2742 N   CYS 418  32.726 52.041  3.905 1.00 32.19 CI
ATOM 2743 H   CYS 418  31.748 52.017  3.860 1.00  0.00
ATOM 2744 CA  CYS 418  33.499 51.119  3.103 1.00 33.67 CI
ATOM 2745 CB  CYS 418  32.657 50.250  2.226 1.00 33.85 CI
ATOM 2746 SG  CYS 418  31.623 49.208  3.246 1.00 37.80 CI
ATOM 2747 C   CYS 418  34.446 51.818  2.170 1.00 34.80 CI
ATOM 2748 O   CYS 418  35.626 51.441  2.173 1.00 36.47 CI
ATOM 2749 N   LEU 419  34.009 52.820  1.377 1.00 35.00 CI
ATOM 2750 H   LEU 419  33.082 53.131  1.460 1.00  0.00
ATOM 2751 CA  LEU 419  34.886 53.446  0.375 1.00 34.14 CI
ATOM 2752 CB  LEU 419  34.062 54.484 -0.413 1.00 37.09 CI
ATOM 2753 CG  LEU 419  32.866 53.853 -1.244 1.00 39.61 CI
ATOM 2754 CD1 LEU 419  31.866 54.918 -1.609 1.00 39.24 CI
ATOM 2755 CD2 LEU 419  33.349 53.207 -2.553 1.00 40.02 CI
ATOM 2756 C   LEU 419  36.102 54.041  1.047 1.00 32.33 CI
ATOM 2757 O   LEU 419  37.198 53.973  0.549 1.00 31.60 CI
ATOM 2758 N   GLU 420  35.974 54.483  2.273 1.00 31.92 CI
ATOM 2759 H   GLU 420  35.068 54.528  2.648 1.00  0.00
ATOM 2760 CA  GLU 420  37.078 54.905  3.092 1.00 31.79 CI
ATOM 2761 CB  GLU 420  36.477 55.462  4.344 1.00 34.29 CI
ATOM 2762 CG  GLU 420  37.430 56.240  5.185 1.00 38.66 CI
ATOM 2763 CD  GLU 420  36.952 56.499  6.609 1.00 45.20 CI
ATOM 2764 OE1 GLU 420  37.873 56.849  7.367 1.00 45.67 CI
ATOM 2765 OE2 GLU 420  35.745 56.345  6.954 1.00 44.21 CI
ATOM 2766 C   GLU 420  38.043 53.763  3.423 1.00 31.87 CI
ATOM 2767 O   GLU 420  39.253 53.949  3.270 1.00 32.82 CI
ATOM 2768 N   GLN 421  37.553 52.624  3.954 1.00 30.46 CI
ATOM 2769 H   GLN 421  36.583 52.556  4.098 1.00  0.00
ATOM 2770 CA  GLN 421  38.366 51.461  4.283 1.00 29.34 CI

ATOM 2771 CB   GLN 421  37.545 50.389  4.984 1.00 30.88 CI
ATOM 2772 CG   GLN 421  37.308 50.634  6.463 1.00 33.58 CI
ATOM 2773 CD   GLN 421  36.320 49.625  7.058 1.00 37.89 CI
ATOM 2774 OE1  GLN 421  35.357 49.236  6.398 1.00 43.18 CI
ATOM 2775 NE2  GLN 421  36.427 49.095  8.275 1.00 37.13 CI
ATOM 2776 HE21 GLN 421  35.695 48.505  8.556 1.00  0.00
ATOM 2777 HE22 GLN 421  37.207 49.330  8.812 1.00  0.00
ATOM 2778 C    GLN 421  38.991 50.862  3.026 1.00 27.36 CI
ATOM 2779 O    GLN 421  40.152 50.445  3.099 1.00 29.09 CI
ATOM 2780 N    VAL 422  38.379 50.845  1.847 1.00 23.57 CI
ATOM 2781 H    VAL 422  37.448 51.138  1.803 1.00  0.00
ATOM 2782 CA   VAL 422  39.077 50.420  0.651 1.00 23.52 CI
ATOM 2783 CB   VAL 422  38.163 50.636 -0.556 1.00 22.67 CI
ATOM 2784 CG1  VAL 422  38.873 50.455 -1.868 1.00 21.56 CI
ATOM 2785 CG2  VAL 422  37.057 49.610 -0.465 1.00 26.79 CI
ATOM 2786 C    VAL 422  40.353 51.254  0.514 1.00 26.22 CI
ATOM 2787 O    VAL 422  41.458 50.708  0.508 1.00 28.77 CI
ATOM 2788 N    ARG 423  40.275 52.599  0.575 1.00 27.49 CI
ATOM 2789 H    ARG 423  39.402 53.016  0.735 1.00  0.00
ATOM 2790 CA   ARG 423  41.436 53.456  0.346 1.00 25.91 CI
ATOM 2791 CB   ARG 423  41.098 54.943  0.312 1.00 24.39 CI
ATOM 2792 CG   ARG 423  40.167 55.366 -0.807 1.00 22.81 CI
ATOM 2793 CD   ARG 423  40.525 54.798 -2.172 1.00 25.55 CI
ATOM 2794 NE   ARG 423  39.707 55.387 -3.216 1.00 25.38 CI
ATOM 2795 HE   ARG 423  39.168 56.173 -2.989 1.00  0.00
ATOM 2796 CZ   ARG 423  39.629 54.928 -4.466 1.00 27.32 CI
ATOM 2797 NH1  ARG 423  40.264 53.857 -4.949 1.00 26.37 CI
ATOM 2798 HH11 ARG 423  40.884 53.341 -4.365 1.00  0.00
ATOM 2799 HH12 ARG 423  40.150 53.595 -5.907 1.00  0.00
ATOM 2800 NH2  ARG 423  38.960 55.682 -5.325 1.00 30.38 CI
ATOM 2801 HH21 ARG 423  38.539 56.537 -5.023 1.00  0.00
ATOM 2802 HH22 ARG 423  38.865 55.385 -6.275 1.00  0.00
ATOM 2803 C    ARG 423  42.429 53.241  1.432 1.00 23.60 CI
ATOM 2804 O    ARG 423  43.594 53.147  1.127 1.00 24.37 CI
ATOM 2805 N    LYS 424  42.065 53.050  2.668 1.00 24.38 CI
ATOM 2806 H    LYS 424  41.109 53.051  2.890 1.00  0.00
```

FIG. 5NN

```
ATOM 2807 CA  LYS 424   43.043 52.855  3.722 1.00 25.12  C
ATOM 2808 CB  LYS 424   42.352 52.791  5.051 1.00 23.89  C
ATOM 2809 CG  LYS 424   43.312 52.936  6.190 1.00 28.56  C
ATOM 2810 CD  LYS 424   42.579 52.580  7.486 1.00 35.51  C
ATOM 2811 CE  LYS 424   41.338 53.425  7.853 1.00 40.33  C
ATOM 2812 NZ  LYS 424   40.519 52.722  8.834 1.00 42.23  C
ATOM 2813 HZ1 LYS 424   41.079 52.559  9.695 1.00  0.00  C
ATOM 2814 HZ2 LYS 424   40.208 51.814  8.435 1.00  0.00  C
ATOM 2815 HZ3 LYS 424   39.689 53.306  9.065 1.00  0.00  C
ATOM 2816 C   LYS 424   43.761 51.547  3.462 1.00 27.10  C
ATOM 2817 O   LYS 424   44.923 51.425  3.848 1.00 30.64  C
ATOM 2818 N   ILE 425   43.190 50.542  2.794 1.00 26.83  C
ATOM 2819 H   ILE 425   42.260 50.607  2.488 1.00  0.00  C
ATOM 2820 CA  ILE 425   43.949 49.312  2.561 1.00 25.46  C
ATOM 2821 CB  ILE 425   42.965 48.093  2.336 1.00 24.91  C
ATOM 2822 CG2 ILE 425   43.654 46.786  1.995 1.00 22.01  C
ATOM 2823 CG1 ILE 425   42.229 47.909  3.633 1.00 25.34  C
ATOM 2824 CD  ILE 425   40.885 47.169  3.432 1.00 25.68  C
ATOM 2825 C   ILE 425   44.824 49.549  1.346 1.00 23.84  C
ATOM 2826 O   ILE 425   45.959 49.069  1.316 1.00 24.57  C
ATOM 2827 N   GLN 426   44.361 50.267  0.323 1.00 23.28  C
ATOM 2828 H   GLN 426   43.451 50.630  0.393 1.00  0.00  C
ATOM 2829 CA  GLN 426   45.164 50.531 -0.887 1.00 24.13  C
ATOM 2830 CB  GLN 426   44.421 51.344 -1.896 1.00 24.04  C
ATOM 2831 CG  GLN 426   43.275 50.539 -2.396 1.00 23.56  C
ATOM 2832 CD  GLN 426   42.446 51.105 -3.511 1.00 23.92  C
ATOM 2833 OE1 GLN 426   41.704 52.047 -3.345 1.00 25.34  C
ATOM 2834 NE2 GLN 426   42.337 50.509 -4.672 1.00 27.55  C
ATOM 2835 HE21 GLN 426  41.755 50.948 -5.323 1.00  0.00  C
ATOM 2836 HE22 GLN 426  42.850 49.696 -4.851 1.00  0.00  C
ATOM 2837 C   GLN 426   46.404 51.312 -0.488 1.00 26.69  C
ATOM 2838 O   GLN 426   47.486 51.109 -1.046 1.00 29.73  C
ATOM 2839 N   GLY 427   46.300 52.204  0.499 1.00 26.49  C
ATOM 2840 H   GLY 427   45.410 52.414  0.854 1.00  0.00  C
ATOM 2841 CA  GLY 427   47.446 52.894  1.022 1.00 24.25  C
ATOM 2842 C   GLY 427   48.467 51.913  1.589 1.00 23.08  C
ATOM 2843 O   GLY 427   49.597 51.921  1.106 1.00 22.28  C
ATOM 2844 N   ASP 428   48.107 51.073  2.575 1.00 22.75  C
ATOM 2845 H   ASP 428   47.189 51.111  2.918 1.00  0.00  C
ATOM 2846 CA  ASP 428   49.039 50.108  3.131 1.00 23.87  C
ATOM 2847 CB  ASP 428   48.415 49.199  4.117 1.00 26.52  C
ATOM 2848 CG  ASP 428   47.437 49.779  5.097 1.00 28.84  C
ATOM 2849 OD1 ASP 428   46.420 49.151  5.265 1.00 31.81  C
ATOM 2850 OD2 ASP 428   47.662 50.804  5.716 1.00 30.77  C
ATOM 2851 C   ASP 428   49.626 49.191  2.063 1.00 24.16  C
ATOM 2852 O   ASP 428   50.812 48.896  2.088 1.00 26.17  C
ATOM 2853 N   GLY 429   48.840 48.822  1.069 1.00 23.01  C
ATOM 2854 H   GLY 429   47.905 49.113  1.071 1.00  0.00  C
ATOM 2855 CA  GLY 429   49.289 47.964  0.029 1.00 25.44  C
ATOM 2856 C   GLY 429   50.405 48.649 -0.716 1.00 27.39  C
ATOM 2857 O   GLY 429   51.528 48.135 -0.741 1.00 28.51  C
ATOM 2858 N   ALA 430   50.127 49.840 -1.271 1.00 28.26  C
ATOM 2859 H   ALA 430   49.216 50.185 -1.172 1.00  0.00  C
ATOM 2860 CA  ALA 430   51.094 50.643 -2.015 1.00 26.04  C
ATOM 2861 CB  ALA 430   50.490 51.976 -2.407 1.00 27.93  C
ATOM 2862 C   ALA 430   52.300 50.927 -1.133 1.00 25.19  C
ATOM 2863 O   ALA 430   53.393 51.053 -1.655 1.00 25.43  C
ATOM 2864 N   ALA 431   52.171 50.979  0.186 1.00 24.05  C
ATOM 2865 H   ALA 431   51.279 50.872  0.579 1.00  0.00  C
ATOM 2866 CA  ALA 431   53.295 51.213  1.035 1.00 26.29  C
ATOM 2867 CB  ALA 431   52.874 51.522  2.458 1.00 24.14  C
ATOM 2868 C   ALA 431   54.139 49.972  1.073 1.00 29.82  C
ATOM 2869 O   ALA 431   55.360 50.085  0.959 1.00 31.97  C
ATOM 2870 N   LEU 432   53.562 48.777  1.203 1.00 31.87  C
ATOM 2871 H   LEU 432   52.585 48.726  1.279 1.00  0.00  C
ATOM 2872 CA  LEU 432   54.337 47.540  1.165 1.00 33.92  C
ATOM 2873 CB  LEU 432   53.430 46.315  1.301 1.00 37.42  C
ATOM 2874 CG  LEU 432   54.063 44.952  1.574 1.00 37.40  C
ATOM 2875 CD1 LEU 432   54.751 44.949  2.950 1.00 38.10  C
ATOM 2876 CD2 LEU 432   52.966 43.901  1.492 1.00 36.27  C
ATOM 2877 C   LEU 432   55.096 47.404 -0.146 1.00 33.74  C
ATOM 2878 O   LEU 432   56.306 47.179 -0.138 1.00 33.29  C
```

FIG.500

```
ATOM 2879 N   GLN  433  54.402 47.564 -1.276 1.00 34.57 C
ATOM 2880 H   GLN  433  53.439 47.733 -1.186 1.00  0.00 C
ATOM 2881 CA  GLN  433  55.002 47.526 -2.600 1.00 35.83 C
ATOM 2882 CB  GLN  433  53.999 47.892 -3.664 1.00 35.52 C
ATOM 2883 CG  GLN  433  52.996 46.823 -3.832 1.00 39.40 C
ATOM 2884 CD  GLN  433  52.049 47.097 -4.973 1.00 42.46 C
ATOM 2885 OE1 GLN  433  50.924 47.526 -4.786 1.00 48.22 C
ATOM 2886 NE2 GLN  433  52.376 46.878 -6.225 1.00 44.77 C
ATOM 2887 HE21 GLN 433  53.271 46.540 -6.433 1.00  0.00 C
ATOM 2888 HE22 GLN 433  51.693 47.087 -6.892 1.00  0.00 C
ATOM 2889 C   GLN  433  56.177 48.485 -2.757 1.00 36.48 C
ATOM 2890 O   GLN  433  57.214 48.118 -3.312 1.00 38.08 C
ATOM 2891 N   GLU  434  56.055 49.719 -2.287 1.00 36.11 C
ATOM 2892 H   GLU  434  55.210 49.978 -1.854 1.00  0.00 C
ATOM 2893 CA  GLU  434  57.089 50.719 -2.426 1.00 35.93 C
ATOM 2894 CB  GLU  434  56.408 52.030 -2.068 1.00 41.28 C
ATOM 2895 CG  GLU  434  57.126 53.356 -2.019 1.00 43.07 C
ATOM 2896 CD  GLU  434  57.832 53.516 -0.698 1.00 45.70 C
ATOM 2897 OE1 GLU  434  57.190 53.538  0.367 1.00 49.33 C
ATOM 2898 OE2 GLU  434  59.051 53.579 -0.760 1.00 45.45 C
ATOM 2899 C   GLU  434  58.257 50.348 -1.548 1.00 34.00 C
ATOM 2900 O   GLU  434  59.388 50.481 -1.983 1.00 32.93 C
ATOM 2901 N   LYS  435  58.067 49.860 -0.330 1.00 34.34 C
ATOM 2902 H   LYS  435  57.146 49.837  0.014 1.00  0.00 C
ATOM 2903 CA  LYS  435  59.151 49.358  0.511 1.00 34.56 C
ATOM 2904 CB  LYS  435  58.577 49.010  1.847 1.00 33.89 C
ATOM 2905 CG  LYS  435  58.357 50.231  2.709 1.00 36.71 C
ATOM 2906 CD  LYS  435  58.244 49.748  4.137 1.00 40.31 C
ATOM 2907 CE  LYS  435  58.293 50.861  5.213 1.00 45.32 C
ATOM 2908 NZ  LYS  435  58.494 50.325  6.575 1.00 47.31 C
ATOM 2909 HZ1 LYS  435  59.388 49.795  6.611 1.00  0.00 C
ATOM 2910 HZ2 LYS  435  57.708 49.689  6.818 1.00  0.00 C
ATOM 2911 HZ3 LYS  435  58.534 51.109  7.257 1.00  0.00 C
ATOM 2912 C   LYS  435  59.906 48.135 -0.065 1.00 36.10 C
ATOM 2913 O   LYS  435  61.139 48.036 -0.012 1.00 37.08 C
ATOM 2914 N   LEU  436  59.215 47.168 -0.665 1.00 36.28 C

ATOM 2915 H   LEU  436  58.235 47.245 -0.651 1.00  0.00 C
ATOM 2916 CA  LEU  436  59.793 45.994 -1.304 1.00 34.25 C
ATOM 2917 CB  LEU  436  58.655 45.076 -1.753 1.00 33.41 C
ATOM 2918 CG  LEU  436  57.920 44.327 -0.610 1.00 34.72 C
ATOM 2919 CD1 LEU  436  56.764 43.538 -1.181 1.00 33.50 C
ATOM 2920 CD2 LEU  436  58.880 43.375  0.117 1.00 36.39 C
ATOM 2921 C   LEU  436  60.669 46.383 -2.467 1.00 33.31 C
ATOM 2922 O   LEU  436  61.756 45.825 -2.647 1.00 33.94 C
ATOM 2923 N   CYS  437  60.220 47.374 -3.222 1.00 32.34 C
ATOM 2924 H   CYS  437  59.290 47.661 -3.097 1.00  0.00 C
ATOM 2925 CA  CYS  437  60.978 47.949 -4.301 1.00 32.01 C
ATOM 2926 C   CYS  437  62.214 48.704 -3.857 1.00 34.70 C
ATOM 2927 O   CYS  437  63.313 48.599 -4.412 1.00 36.26 C
ATOM 2928 CB  CYS  437  60.094 48.840 -5.008 1.00 30.97 C
ATOM 2929 SG  CYS  437  61.003 49.666 -6.319 1.00 36.22 C
ATOM 2930 N   ALA  438  62.016 49.463 -2.785 1.00 36.35 C
ATOM 2931 H   ALA  438  61.108 49.547 -2.431 1.00  0.00 C
ATOM 2932 CA  ALA  438  63.060 50.226 -2.170 1.00 35.83 C
ATOM 2933 CB  ALA  438  62.440 51.107 -1.153 1.00 36.38 C
ATOM 2934 C   ALA  438  64.065 49.294 -1.527 1.00 37.01 C
ATOM 2935 O   ALA  438  65.132 49.168 -2.092 1.00 39.39 C
ATOM 2936 N   THR  439  63.808 48.591 -0.422 1.00 36.59 C
ATOM 2937 H   THR  439  62.947 48.723  0.014 1.00  0.00 C
ATOM 2938 CA  THR  439  64.742 47.669  0.223 1.00 35.70 C
ATOM 2939 CB  THR  439  64.073 47.042  1.400 1.00 35.34 C
ATOM 2940 OG1 THR  439  63.323 48.048  2.040 1.00 38.31 C
ATOM 2941 HG1 THR  439  62.419 47.999  1.706 1.00  0.00 C
ATOM 2942 CG2 THR  439  65.039 46.479  2.369 1.00 36.50 C
ATOM 2943 C   THR  439  65.331 46.517 -0.590 1.00 36.10 C
ATOM 2944 O   THR  439  66.448 46.093 -0.312 1.00 36.51 C
ATOM 2945 N   TYR  440  64.603 45.917 -1.548 1.00 36.02 C
ATOM 2946 H   TYR  440  63.751 46.319 -1.822 1.00  0.00 C
ATOM 2947 CA  TYR  440  65.057 44.691 -2.198 1.00 34.28 C
ATOM 2948 CB  TYR  440  64.175 43.480 -1.878 1.00 33.99 C
ATOM 2949 CG  TYR  440  64.016 43.240 -0.397 1.00 34.14 C
ATOM 2950 CD1 TYR  440  62.773 43.230  0.169 1.00 35.16 C
```

FIG.5PP

```
ATOM 2951 CE1 TYR 440 62.625 43.037  1.532 1.00 36.66 Cl
ATOM 2952 CD2 TYR 440 65.126 43.064  0.385 1.00 37.83 Cl
ATOM 2953 CE2 TYR 440 64.992 42.881  1.752 1.00 39.02 Cl
ATOM 2954 CZ  TYR 440 63.741 42.864  2.317 1.00 37.34 Cl
ATOM 2955 OH  TYR 440 63.637 42.649  3.678 1.00 37.56 Cl
ATOM 2956 HH  TYR 440 64.498 42.343  3.988 1.00  0.00 Cl
ATOM 2957 C   TYR 440 65.088 44.768 -3.681 1.00 34.07 Cl
ATOM 2958 O   TYR 440 65.598 43.823 -4.267 1.00 35.54 Cl
ATOM 2959 N   LYS 441 64.627 45.833 -4.330 1.00 33.18 Cl
ATOM 2960 H   LYS 441 64.345 46.623 -3.822 1.00  0.00 Cl
ATOM 2961 CA  LYS 441 64.595 45.957 -5.763 1.00 30.44 Cl
ATOM 2962 CB  LYS 441 65.983 45.759 -6.364 1.00 33.76 Cl
ATOM 2963 CG  LYS 441 66.729 47.080 -6.407 1.00 39.59 Cl
ATOM 2964 CD  LYS 441 67.273 47.497 -5.045 1.00 47.69 Cl
ATOM 2965 CE  LYS 441 67.503 49.028 -4.984 1.00 53.37 Cl
ATOM 2966 NZ  LYS 441 66.267 49.780 -5.240 1.00 57.64 Cl
ATOM 2967 HZ1 LYS 441 65.568 49.549 -4.506 1.00  0.00 Cl
ATOM 2968 HZ2 LYS 441 65.885 49.525 -6.173 1.00  0.00 Cl
ATOM 2969 HZ3 LYS 441 66.468 50.801 -5.219 1.00  0.00 Cl
ATOM 2970 C   LYS 441 63.629 45.015 -6.425 1.00 28.86 Cl
ATOM 2971 O   LYS 441 63.791 44.688 -7.603 1.00 29.95 Cl
ATOM 2972 N   LEU 442 62.556 44.601 -5.749 1.00 27.58 Cl
ATOM 2973 H   LEU 442 62.392 44.924 -4.837 1.00  0.00 Cl
ATOM 2974 CA  LEU 442 61.554 43.780 -6.402 1.00 28.82 Cl
ATOM 2975 CB  LEU 442 60.947 42.694 -5.466 1.00 26.98 Cl
ATOM 2976 CG  LEU 442 61.905 41.634 -4.847 1.00 27.75 Cl
ATOM 2977 CD1 LEU 442 61.133 40.643 -4.009 1.00 24.29 Cl
ATOM 2978 CD2 LEU 442 62.667 40.932 -5.963 1.00 19.72 Cl
ATOM 2979 C   LEU 442 60.575 44.892 -6.635 1.00 30.59 Cl
ATOM 2980 O   LEU 442 59.811 45.261 -5.741 1.00 32.36 Cl
ATOM 2981 N   CYS 443 60.700 45.506 -7.804 1.00 32.15 Cl
ATOM 2982 H   CYS 443 61.423 45.199 -8.389 1.00  0.00 Cl
ATOM 2983 CA  CYS 443 59.866 46.645 -8.191 1.00 32.69 Cl
ATOM 2984 C   CYS 443 58.807 46.380 -9.217 1.00 33.43 Cl
ATOM 2985 O   CYS 443 58.051 47.288 -9.465 1.00 34.10 Cl
ATOM 2986 CB  CYS 443 60.715 47.800 -8.743 1.00 30.74 Cl
ATOM 2987 SG  CYS 443 61.938 48.345 -7.519 1.00 32.96 Cl
ATOM 2988 N   HIS 444 58.649 45.260 -9.911 1.00 35.65 Cl
ATOM 2989 H   HIS 444 59.147 44.445 -9.659 1.00  0.00 Cl
ATOM 2990 CA  HIS 444 57.662 45.172 -10.975 1.01 37.75 Cl
ATOM 2991 CB  HIS 444 58.329 45.224 -12.330 1.00 37.09 Cl
ATOM 2992 CG  HIS 444 59.149 46.476 -12.560 1.00 41.36 Cl
ATOM 2993 CD2 HIS 444 60.434 46.664 -12.075 1.00 41.40 Cl
ATOM 2994 ND1 HIS 444 58.811 47.563 -13.261 1.00 41.74 Cl
ATOM 2995 HD1 HIS 444 57.892 47.890 -13.410 1.00  0.00 Cl
ATOM 2996 CE1 HIS 444 59.850 48.372 -13.217 1.00 42.00 Cl
ATOM 2997 NE2 HIS 444 60.817 47.832 -12.502 1.00 41.38 Cl
ATOM 2998 HE2 HIS 444 61.690 48.248 -12.334 1.00  0.00 Cl
ATOM 2999 C   HIS 444 56.889 43.871 -10.878 1.00 40.10 Cl
ATOM 3000 O   HIS 444 57.461 42.867 -11.309 1.00 40.15 Cl
ATOM 3001 N   PRO 445 55.615 43.752 -10.406 1.00 42.06 Cl
ATOM 3002 CD  PRO 445 54.738 44.836 -9.937 1.00 41.56 Cl
ATOM 3003 CA  PRO 445 54.913 42.497 -10.276 1.00 40.90 Cl
ATOM 3004 CB  PRO 445 53.569 42.882 -9.730 1.00 39.35 Cl
ATOM 3005 CG  PRO 445 53.364 44.274 -10.215 1.00 39.35 Cl
ATOM 3006 C   PRO 445 54.868 41.782 -11.600 1.00 42.18 Cl
ATOM 3007 O   PRO 445 54.769 40.571 -11.569 1.00 45.69 Cl
ATOM 3008 N   GLU 446 55.082 42.380 -12.769 1.00 41.64 Cl
ATOM 3009 H   GLU 446 55.320 43.320 -12.761 1.00  0.00 Cl
ATOM 3010 CA  GLU 446 55.025 41.656 -14.029 1.00 42.05 Cl
ATOM 3011 CB  GLU 446 54.967 42.639 -15.183 1.00 47.06 Cl
ATOM 3012 CG  GLU 446 54.109 43.925 -14.992 1.00 56.71 Cl
ATOM 3013 CD  GLU 446 54.728 45.083 -14.162 1.00 62.28 Cl
ATOM 3014 OE1 GLU 446 54.100 45.472 -13.178 1.00 66.26 Cl
ATOM 3015 OE2 GLU 446 55.818 45.604 -14.473 1.00 65.55 Cl
ATOM 3016 C   GLU 446 56.237 40.722 -14.197 1.00 40.44 Cl
ATOM 3017 O   GLU 446 56.186 39.708 -14.904 1.00 41.66 Cl
ATOM 3018 N   GLU 447 57.360 40.995 -13.538 1.00 37.89 Cl
ATOM 3019 H   GLU 447 57.394 41.809 -12.999 1.00  0.00 Cl
ATOM 3020 CA  GLU 447 58.519 40.096 -13.509 1.00 36.73 Cl
ATOM 3021 CB  GLU 447 59.750 40.810 -12.976 1.00 34.60 Cl
ATOM 3022 CG  GLU 447 60.320 41.883 -13.850 1.00 35.27 Cl
```

ATOM	3023	CD	GLU	447	61.450	42.699	-13.197	1.00 36.14	Cl
ATOM	3024	OE1	GLU	447	62.240	43.286	-13.939	1.00 37.31	Cl
ATOM	3025	OE2	GLU	447	61.541	42.782	-11.970	1.00 32.80	Cl
ATOM	3026	C	GLU	447	58.311	38.850	-12.599	1.00 36.31	Cl
ATOM	3027	O	GLU	447	59.113	37.911	-12.592	1.00 36.33	Cl
ATOM	3028	N	LEU	448	57.273	38.763	-11.769	1.00 33.81	Cl
ATOM	3029	H	LEU	448	56.554	39.431	-11.802	1.00 0.00	Cl
ATOM	3030	CA	LEU	448	57.145	37.691	-10.839	1.00 31.88	Cl
ATOM	3031	CB	LEU	448	57.080	38.299	-9.484	1.00 29.29	Cl
ATOM	3032	CG	LEU	448	58.008	39.432	-9.140	1.00 29.81	Cl
ATOM	3033	CD1	LEU	448	57.907	39.863	-7.684	1.00 26.02	Cl
ATOM	3034	CD2	LEU	448	59.396	38.931	-9.392	1.00 31.13	Cl
ATOM	3035	C	LEU	448	55.863	36.977	-11.165	1.00 33.75	Cl
ATOM	3036	O	LEU	448	55.436	36.145	-10.382	1.00 33.96	Cl
ATOM	3037	N	VAL	449	55.166	37.233	-12.263	1.00 36.99	Cl
ATOM	3038	H	VAL	449	55.580	37.800	-12.942	1.00 0.00	Cl
ATOM	3039	CA	VAL	449	53.819	36.701	-12.472	1.00 41.46	Cl
ATOM	3040	CB	VAL	449	53.157	37.546	-13.625	1.00 41.56	Cl
ATOM	3041	CG1	VAL	449	54.002	37.614	-14.880	1.00 42.22	Cl
ATOM	3042	CG2	VAL	449	51.921	36.858	-14.112	1.00 42.01	Cl
ATOM	3043	C	VAL	449	53.760	35.192	-12.733	1.00 44.81	Cl
ATOM	3044	O	VAL	449	52.866	34.469	-12.227	1.00 44.54	Cl
ATOM	3045	N	LEU	450	54.716	34.669	-13.515	1.00 47.21	Cl
ATOM	3046	H	LEU	450	55.416	35.260	-13.870	1.00 0.00	Cl
ATOM	3047	CA	LEU	450	54.771	33.243	-13.781	1.00 50.57	Cl
ATOM	3048	CB	LEU	450	55.942	32.894	-14.628	1.00 50.75	Cl
ATOM	3049	CG	LEU	450	56.148	33.488	-15.994	1.00 52.39	Cl
ATOM	3050	CD1	LEU	450	57.152	32.586	-16.673	1.00 53.05	Cl
ATOM	3051	CD2	LEU	450	54.882	33.534	-16.833	1.00 54.10	Cl
ATOM	3052	C	LEU	450	54.911	32.468	-12.471	1.00 53.83	Cl
ATOM	3053	O	LEU	450	54.297	31.406	-12.266	1.00 55.62	Cl
ATOM	3054	N	LEU	451	55.685	33.097	-11.575	1.00 55.46	Cl
ATOM	3055	H	LEU	451	56.073	33.954	-11.849	1.00 0.00	Cl
ATOM	3056	CA	LEU	451	55.998	32.654	-10.223	1.00 56.01	Cl
ATOM	3057	CB	LEU	451	57.137	33.542	-9.731	1.00 55.80	Cl
ATOM	3058	CG	LEU	451	57.745	33.278	-8.394	1.00 56.96	Cl
ATOM	3059	CD1	LEU	451	58.833	32.284	-8.653	1.00 59.12	Cl
ATOM	3060	CD2	LEU	451	58.369	34.511	-7.751	1.00 58.27	Cl
ATOM	3061	C	LEU	451	54.785	32.700	-9.280	1.00 55.96	Cl
ATOM	3062	O	LEU	451	54.717	31.935	-8.319	1.00 53.74	Cl
ATOM	3063	N	GLY	452	53.774	33.533	-9.522	1.00 57.52	Cl
ATOM	3064	H	GLY	452	53.889	34.241	-10.191	1.00 0.00	Cl
ATOM	3065	CA	GLY	452	52.567	33.515	-8.710	1.00 60.66	Cl
ATOM	3066	C	GLY	452	51.942	32.137	-8.772	1.00 63.64	Cl
ATOM	3067	O	GLY	452	51.476	31.593	-7.782	1.00 62.60	Cl
ATOM	3068	N	HIS	453	52.089	31.545	-9.969	1.00 68.46	Cl
ATOM	3069	H	HIS	453	52.628	32.040	-10.618	1.00 0.00	Cl
ATOM	3070	CA	HIS	453	51.606	30.205	-10.326	1.00 72.27	Cl
ATOM	3071	CB	HIS	453	51.785	29.908	-11.828	1.00 73.84	Cl
ATOM	3072	CG	HIS	453	51.421	31.061	-12.777	1.00 77.81	Cl
ATOM	3073	CD2	HIS	453	50.599	32.148	-12.498	1.00 79.29	Cl
ATOM	3074	ND1	HIS	453	51.886	31.244	-14.012	1.00 79.84	Cl
ATOM	3075	HD1	HIS	453	52.617	30.739	-14.425	1.00 0.00	Cl
ATOM	3076	CE1	HIS	453	51.385	32.382	-14.470	1.00 81.11	Cl
ATOM	3077	NE2	HIS	453	50.613	32.923	-13.551	1.00 79.85	Cl
ATOM	3078	HE2	HIS	453	50.230	33.825	-13.586	1.00 0.00	Cl
ATOM	3079	C	HIS	453	52.454	29.235	-9.515	1.00 73.43	Cl
ATOM	3080	O	HIS	453	51.875	28.531	-8.692	1.00 73.56	Cl
ATOM	3081	N	SER	454	53.785	29.207	-9.651	1.00 74.64	Cl
ATOM	3082	H	SER	454	54.214	29.739	-10.351	1.00 0.00	Cl
ATOM	3083	CA	SER	454	54.639	28.411	-8.765	1.00 77.07	Cl
ATOM	3084	CB	SER	454	56.123	28.762	-8.980	1.00 77.34	Cl
ATOM	3085	OG	SER	454	57.095	27.715	-9.124	1.00 75.28	Cl
ATOM	3086	HG	SER	454	57.149	27.211	-8.306	1.00 0.00	Cl
ATOM	3087	C	SER	454	54.332	28.608	-7.262	1.00 78.84	Cl
ATOM	3088	O	SER	454	54.270	27.617	-6.535	1.00 80.57	Cl
ATOM	3089	N	LEU	455	54.070	29.789	-6.693	1.00 79.72	Cl
ATOM	3090	H	LEU	455	53.956	30.582	-7.250	1.00 0.00	Cl
ATOM	3091	CA	LEU	455	53.849	29.915	-5.257	1.00 80.43	Cl
ATOM	3092	CB	LEU	455	54.085	31.347	-4.838	1.00 80.20	Cl
ATOM	3093	CG	LEU	455	55.389	31.981	-5.269	1.00 81.67	Cl
ATOM	3094	CD1	LEU	455	55.254	33.494	-5.419	1.00 81.36	Cl

FIG. 500

FIG.5RR

```
ATOM 3095 CD2 LEU 455    56.431 31.579  -4.264 1.00 82.26 C1
ATOM 3096 C   LEU 455    52.438 29.510  -4.848 1.00 81.56 C1
ATOM 3097 O   LEU 455    52.038 29.893  -3.741 1.00 82.22 C1
ATOM 3098 N   GLY 456    51.653 28.816  -5.708 1.00 81.89 C1
ATOM 3099 H   GLY 456    52.026 28.592  -6.584 1.00 0.00  C1
ATOM 3100 CA  GLY 456    50.269 28.361  -5.467 1.00 82.22 C1
ATOM 3101 C   GLY 456    49.220 29.386  -4.973 1.00 82.56 C1
ATOM 3102 O   GLY 456    48.268 28.989  -4.276 1.00 82.38 C1
ATOM 3103 N   ILE 457    49.342 30.697  -5.286 1.00 82.54 C1
ATOM 3104 H   ILE 457    50.075 30.942  -5.894 1.00 0.00  C1
ATOM 3105 CA  ILE 457    48.435 31.761  -4.824 1.00 81.63 C1
ATOM 3106 CB  ILE 457    49.110 33.157  -5.086 1.00 80.69 C1
ATOM 3107 CG2 ILE 457    48.218 34.305  -4.662 1.00 79.76 C1
ATOM 3108 CG1 ILE 457    50.369 33.275  -4.253 1.00 79.82 C1
ATOM 3109 CD  ILE 457    51.506 33.868  -5.081 1.00 77.89 C1
ATOM 3110 C   ILE 457    47.048 31.698  -5.472 1.00 81.70 C1
ATOM 3111 O   ILE 457    46.903 31.761  -6.700 1.00 82.57 C1
ATOM 3112 N   PRO 458    45.963 31.583  -4.705 1.00 81.40 C1
ATOM 3113 CD  PRO 458    45.959 31.225  -3.278 1.00 81.21 C1
ATOM 3114 CA  PRO 458    44.607 31.643  -5.264 1.00 80.74 C1
ATOM 3115 CB  PRO 458    43.779 30.942  -4.157 1.00 81.12 C1
ATOM 3116 CG  PRO 458    44.757 30.293  -3.173 1.00 80.47 C1
ATOM 3117 C   PRO 458    44.120 33.063  -5.648 1.00 79.70 C1
ATOM 3118 O   PRO 458    43.674 33.736  -4.718 1.00 80.10 C1
ATOM 3119 N   TRP 459    44.171 33.662  -6.861 1.00 78.19 C1
ATOM 3120 H   TRP 459    44.614 33.185  -7.591 1.00 0.00  C1
ATOM 3121 CA  TRP 459    43.543 34.986  -7.092 1.00 77.73 C1
ATOM 3122 CB  TRP 459    43.802 35.428  -8.522 1.00 78.71 C1
ATOM 3123 CG  TRP 459    43.054 36.677  -9.017 1.00 81.37 C1
ATOM 3124 CD2 TRP 459    41.802 36.771  -9.618 1.00 82.89 C1
ATOM 3125 CE2 TRP 459    41.717 38.139  -9.883 1.00 84.21 C1
ATOM 3126 CE3 TRP 459    40.738 35.960  -9.983 1.00 84.28 C1
ATOM 3127 CD1 TRP 459    43.661 37.899  -8.925 1.00 83.89 C1
ATOM 3128 NE1 TRP 459    42.828 38.765  -9.460 1.00 85.23 C1
ATOM 3129 HE1 TRP 459    42.944 39.738  -9.483 1.00 0.00  C1
ATOM 3130 CZ2 TRP 459    40.615 38.727 -10.494 1.00 84.17 C1

ATOM 3131 CZ3 TRP 459    39.630 36.538 -10.597 1.00 84.56 C1
ATOM 3132 CH2 TRP 459    39.562 37.904 -10.852 1.00 84.83 C1
ATOM 3133 C   TRP 459    42.009 35.013  -6.827 1.00 77.31 C1
ATOM 3134 O   TRP 459    41.202 34.244  -7.376 1.00 76.38 C1
ATOM 3135 N   ALA 460    41.557 35.969  -6.020 1.00 76.81 C1
ATOM 3136 H   ALA 460    42.187 36.640  -5.689 1.00 0.00  C1
ATOM 3137 CA  ALA 460    40.158 36.044  -5.613 1.00 76.44 C1
ATOM 3138 CB  ALA 460    40.072 36.724  -4.243 1.00 75.51 C1
ATOM 3139 C   ALA 460    39.237 36.784  -6.588 1.00 76.29 C1
ATOM 3140 O   ALA 460    39.449 37.976  -6.833 1.00 76.98 C1
ATOM 3141 N   PRO 461    38.217 36.147  -7.187 1.00 76.26 C1
ATOM 3142 CD  PRO 461    38.104 34.684  -7.245 1.00 75.88 C1
ATOM 3143 CA  PRO 461    37.242 36.793  -8.068 1.00 75.46 C1
ATOM 3144 CB  PRO 461    36.605 35.605  -8.755 1.00 75.71 C1
ATOM 3145 CG  PRO 461    36.703 34.458  -7.767 1.00 75.60 C1
ATOM 3146 C   PRO 461    36.221 37.803  -7.545 1.00 75.72 C1
ATOM 3147 O   PRO 461    35.677 37.734  -6.440 1.00 73.66 C1
ATOM 3148 N   LEU 462    35.996 38.767  -8.449 1.00 77.19 C1
ATOM 3149 H   LEU 462    36.516 38.723  -9.277 1.00 0.00  C1
ATOM 3150 CA  LEU 462    35.069 39.891  -8.275 1.00 78.87 C1
ATOM 3151 CB  LEU 462    35.674 40.984  -7.360 1.00 78.32 C1
ATOM 3152 CG  LEU 462    34.786 41.959  -6.558 1.00 78.09 C1
ATOM 3153 CD1 LEU 462    34.051 42.987  -7.406 1.00 78.32 C1
ATOM 3154 CD2 LEU 462    33.767 41.092  -5.828 1.00 78.62 C1
ATOM 3155 C   LEU 462    34.701 40.565  -9.611 1.00 80.63 C1
ATOM 3156 OT1 LEU 462    33.507 40.842  -9.808 1.00 81.74 C1
ATOM 3157 OT2 LEU 462    35.606 40.847 -10.417 1.00 81.39 C1
ATOM 3158 CB  LEU 472    22.074 42.654  -1.426 1.00 62.24 C2
ATOM 3159 CG  LEU 472    22.278 44.145  -1.189 1.00 59.98 C2
ATOM 3160 CD1 LEU 472    23.496 44.325  -0.328 1.00 59.13 C2
ATOM 3161 CD2 LEU 472    22.501 44.883  -2.486 1.00 56.85 C2
ATOM 3162 C   LEU 472    23.504 40.625  -1.996 1.00 63.91 C2
ATOM 3163 O   LEU 472    23.738 39.874  -2.949 1.00 64.90 C2
ATOM 3164 HT1 LEU 472    21.563 41.441  -3.595 1.00 0.00  C2
ATOM 3165 HT2 LEU 472    23.091 41.291  -4.237 1.00 0.00  C2
ATOM 3166 N   LEU 472    22.472 41.930  -3.693 1.00 64.29 C2
```

FIG.5SS

ATOM	3167	HT3	LEU	472	22.358	42.849	-4.160	1.00	0.00	C2
ATOM	3168	CA	LEU	472	23.092	42.037	-2.386	1.00	63.85	C2
ATOM	3169	N	ALA	473	23.652	40.229	-0.733	1.00	63.02	C2
ATOM	3170	H	ALA	473	23.533	40.867	0.002	1.00	0.00	C2
ATOM	3171	CA	ALA	473	24.023	38.881	-0.353	1.00	62.37	C2
ATOM	3172	CB	ALA	473	22.870	37.939	-0.558	1.00	63.65	C2
ATOM	3173	C	ALA	473	25.196	38.354	-1.126	1.00	62.01	C2
ATOM	3174	O	ALA	473	26.301	38.651	-0.715	1.00	63.36	C2
ATOM	3175	N	GLY	474	25.032	37.784	-2.306	1.00	61.43	C2
ATOM	3176	H	GLY	474	24.148	37.818	-2.722	1.00	0.00	C2
ATOM	3177	CA	GLY	474	26.101	37.137	-3.047	1.00	63.80	C2
ATOM	3178	C	GLY	474	27.354	37.950	-3.356	1.00	65.13	C2
ATOM	3179	O	GLY	474	28.482	37.417	-3.257	1.00	66.24	C2
ATOM	3180	N	CYS	475	27.175	39.237	-3.757	1.00	64.88	C2
ATOM	3181	H	CYS	475	26.261	39.550	-3.885	1.00	0.00	C2
ATOM	3182	CA	CYS	475	28.308	40.127	-4.068	1.00	61.84	C2
ATOM	3183	CB	CYS	475	27.925	41.413	-4.806	1.00	63.74	C2
ATOM	3184	SG	CYS	475	29.494	42.075	-5.437	1.00	68.86	C2
ATOM	3185	C	CYS	475	28.995	40.567	-2.795	1.00	57.30	C2
ATOM	3186	O	CYS	475	30.214	40.449	-2.724	1.00	57.14	C2
ATOM	3187	N	LEU	476	28.230	40.983	-1.779	1.00	53.29	C2
ATOM	3188	H	LEU	476	27.264	41.024	-1.885	1.00	0.00	C2
ATOM	3189	CA	LEU	476	28.797	41.315	-0.493	1.00	50.43	C2
ATOM	3190	CB	LEU	476	27.719	41.723	0.523	1.00	45.68	C2
ATOM	3191	CG	LEU	476	27.130	43.165	0.497	1.00	42.80	C2
ATOM	3192	CD1	LEU	476	26.670	43.559	1.896	1.00	36.25	C2
ATOM	3193	CD2	LEU	476	28.180	44.180	0.057	1.00	40.22	C2
ATOM	3194	C	LEU	476	29.546	40.108	0.042	1.00	50.42	C2
ATOM	3195	O	LEU	476	30.614	40.222	0.646	1.00	50.61	C2
ATOM	3196	N	SER	477	29.053	38.922	-0.270	1.00	50.62	C2
ATOM	3197	H	SER	477	28.196	38.860	-0.729	1.00	0.00	C2
ATOM	3198	CA	SER	477	29.721	37.712	0.125	1.00	51.41	C2
ATOM	3199	CB	SER	477	28.778	36.524	-0.051	1.00	53.45	C2
ATOM	3200	OG	SER	477	27.732	36.616	0.926	1.00	57.65	C2
ATOM	3201	HG	SER	477	27.280	37.462	0.828	1.00	0.00	C2
ATOM	3202	C	SER	477	30.978	37.525	-0.681	1.00	50.75	C2
ATOM	3203	O	SER	477	31.980	37.143	-0.068	1.00	51.41	C2
ATOM	3204	N	GLN	478	31.037	37.788	-1.984	1.00	50.21	C2
ATOM	3205	H	GLN	478	30.222	38.056	-2.457	1.00	0.00	C2
ATOM	3206	CA	GLN	478	32.307	37.697	-2.715	1.00	51.37	C2
ATOM	3207	CB	GLN	478	32.064	37.929	-4.166	1.00	53.65	C2
ATOM	3208	CG	GLN	478	31.983	36.570	-4.788	1.00	57.32	C2
ATOM	3209	CD	GLN	478	31.354	36.649	-6.160	1.00	60.47	C2
ATOM	3210	OE1	GLN	478	31.999	36.504	-7.205	1.00	62.26	C2
ATOM	3211	NE2	GLN	478	30.045	36.878	-6.167	1.00	62.16	C2
ATOM	3212	HE21	GLN	478	29.569	36.972	-5.317	1.00	0.00	C2
ATOM	3213	HE22	GLN	478	29.641	36.928	-7.054	1.00	0.00	C2
ATOM	3214	C	GLN	478	33.398	38.670	-2.249	1.00	50.66	C2
ATOM	3215	O	GLN	478	34.584	38.314	-2.217	1.00	50.13	C2
ATOM	3216	N	LEU	479	33.045	39.909	-1.859	1.00	48.78	C2
ATOM	3217	H	LEU	479	32.131	40.223	-2.039	1.00	0.00	C2
ATOM	3218	CA	LEU	479	34.015	40.800	-1.235	1.00	45.87	C2
ATOM	3219	CB	LEU	479	33.434	42.141	-0.827	1.00	47.03	C2
ATOM	3220	CG	LEU	479	32.853	43.083	-1.818	1.00	49.40	C2
ATOM	3221	CD1	LEU	479	32.596	44.393	-1.078	1.00	48.15	C2
ATOM	3222	CD2	LEU	479	33.779	43.258	-3.000	1.00	48.59	C2
ATOM	3223	C	LEU	479	34.505	40.146	0.056	1.00	42.13	C2
ATOM	3224	O	LEU	479	35.695	39.955	0.262	1.00	40.90	C2
ATOM	3225	N	HIS	480	33.609	39.766	0.950	1.00	39.56	C2
ATOM	3226	H	HIS	480	32.658	39.935	0.763	1.00	0.00	C2
ATOM	3227	CA	HIS	480	33.979	39.108	2.179	1.00	37.81	C2
ATOM	3228	CB	HIS	480	32.742	38.714	2.922	1.00	34.29	C2
ATOM	3229	CG	HIS	480	33.094	38.241	4.309	1.00	33.82	C2
ATOM	3230	CD2	HIS	480	33.123	36.932	4.709	1.00	33.44	C2
ATOM	3231	ND1	HIS	480	33.450	38.995	5.344	1.00	34.27	C2
ATOM	3232	HD1	HIS	480	33.505	39.976	5.362	1.00	0.00	C2
ATOM	3233	CE1	HIS	480	33.706	38.223	6.365	1.00	33.80	C2
ATOM	3234	NE2	HIS	480	33.504	36.986	5.965	1.00	37.12	C2
ATOM	3235	HE2	HIS	480	33.637	36.202	6.544	1.00	0.00	C2
ATOM	3236	C	HIS	480	34.836	37.860	1.961	1.00	39.08	C2
ATOM	3237	O	HIS	480	35.716	37.631	2.791	1.00	40.93	C2
ATOM	3238	N	SER	481	34.615	37.029	0.935	1.00	39.24	C2

FIG.5TT

					x	y	z	occ	B	
ATOM	3239	H	SER	481	33.900	37.241	0.305	1.00	0.00	C2
ATOM	3240	CA	SER	481	35.391	35.818	0.683	1.00	38.17	C
ATOM	3241	CB	SER	481	34.813	34.943	-0.420	1.00	40.42	C
ATOM	3242	OG	SER	481	33.454	34.597	-0.137	1.00	47.61	C
ATOM	3243	HG	SER	481	32.898	35.385	-0.162	1.00	0.00	C2
ATOM	3244	C	SER	481	36.724	36.272	0.211	1.00	36.12	C
ATOM	3245	O	SER	481	37.692	35.793	0.765	1.00	36.23	C
ATOM	3246	N	GLY	482	36.786	37.206	-0.744	1.00	36.21	C
ATOM	3247	H	GLY	482	35.956	37.498	-1.168	1.00	0.00	C2
ATOM	3248	CA	GLY	482	38.028	37.792	-1.266	1.00	36.50	C
ATOM	3249	C	GLY	482	38.958	38.296	-0.151	1.00	36.14	C
ATOM	3250	O	GLY	482	40.142	37.936	-0.055	1.00	36.65	C
ATOM	3251	N	LEU	483	38.381	39.084	0.750	1.00	34.04	C
ATOM	3252	H	LEU	483	37.445	39.326	0.608	1.00	0.00	C2
ATOM	3253	CA	LEU	483	39.073	39.593	1.900	1.00	32.07	C
ATOM	3254	CB	LEU	483	38.134	40.442	2.731	1.00	31.17	C
ATOM	3255	CG	LEU	483	37.535	41.687	2.081	1.00	31.11	C
ATOM	3256	CD1	LEU	483	36.757	42.411	3.156	1.00	30.82	C
ATOM	3257	CD2	LEU	483	38.599	42.593	1.480	1.00	29.50	C
ATOM	3258	C	LEU	483	39.600	38.461	2.745	1.00	32.91	C
ATOM	3259	O	LEU	483	40.752	38.498	3.199	1.00	31.25	C
ATOM	3260	N	PHE	484	38.767	37.422	2.925	1.00	34.08	C
ATOM	3261	H	PHE	484	37.900	37.408	2.471	1.00	0.00	C2
ATOM	3262	CA	PHE	484	39.105	36.298	3.788	1.00	34.60	C
ATOM	3263	CB	PHE	484	37.975	35.300	3.925	1.00	37.46	C
ATOM	3264	CG	PHE	484	38.268	34.183	4.897	1.00	40.86	C
ATOM	3265	CD1	PHE	484	38.219	32.884	4.482	1.00	45.62	C
ATOM	3266	CD2	PHE	484	38.528	34.445	6.210	1.00	43.62	C
ATOM	3267	CE1	PHE	484	38.421	31.858	5.395	1.00	47.98	C
ATOM	3268	CE2	PHE	484	38.731	33.427	7.119	1.00	46.78	C
ATOM	3269	CZ	PHE	484	38.677	32.119	6.720	1.00	48.06	C
ATOM	3270	C	PHE	484	40.245	35.602	3.113	1.00	33.92	C
ATOM	3271	O	PHE	484	41.162	35.289	3.826	1.00	34.25	C
ATOM	3272	N	LEU	485	40.326	35.413	1.799	1.00	32.75	C
ATOM	3273	H	LEU	485	39.577	35.717	1.250	1.00	0.00	C2
ATOM	3274	CA	LEU	485	41.475	34.778	1.163	1.00	33.74	C2
ATOM	3275	CB	LEU	485	41.183	34.629	-0.305	1.00	35.35	C
ATOM	3276	CG	LEU	485	42.101	33.962	-1.275	1.00	37.80	C
ATOM	3277	CD1	LEU	485	41.181	33.404	-2.345	1.00	41.44	C
ATOM	3278	CD2	LEU	485	43.125	34.903	-1.899	1.00	40.07	C
ATOM	3279	C	LEU	485	42.740	35.585	1.376	1.00	33.95	C
ATOM	3280	O	LEU	485	43.766	35.060	1.850	1.00	33.84	C
ATOM	3281	N	TYR	486	42.609	36.885	1.034	1.00	33.67	C
ATOM	3282	H	TYR	486	41.757	37.186	0.659	1.00	0.00	C2
ATOM	3283	CA	TYR	486	43.662	37.862	1.242	1.00	31.33	C
ATOM	3284	CB	TYR	486	43.210	39.290	0.714	1.00	35.33	C
ATOM	3285	CG	TYR	486	43.300	39.325	-0.825	1.00	33.37	C
ATOM	3286	CD1	TYR	486	42.154	39.405	-1.579	1.00	32.79	C
ATOM	3287	CE1	TYR	486	42.228	39.290	-2.944	1.00	33.73	C
ATOM	3288	CD2	TYR	486	44.533	39.153	-1.445	1.00	34.59	C
ATOM	3289	CE2	TYR	486	44.618	39.033	-2.818	1.00	34.63	C
ATOM	3290	CZ	TYR	486	43.451	39.096	-3.562	1.00	35.58	C
ATOM	3291	OH	TYR	486	43.484	38.880	-4.942	1.00	38.24	C
ATOM	3292	HH	TYR	486	42.614	39.086	-5.306	1.00	0.00	C2
ATOM	3293	C	TYR	486	44.068	37.905	2.697	1.00	27.39	C
ATOM	3294	O	TYR	486	45.258	38.007	2.942	1.00	26.06	C
ATOM	3295	N	GLN	487	43.270	37.691	3.708	1.00	26.95	C
ATOM	3296	H	GLN	487	42.315	37.545	3.565	1.00	0.00	C2
ATOM	3297	CA	GLN	487	43.835	37.646	5.031	1.00	28.33	C
ATOM	3298	CB	GLN	487	42.690	37.578	6.050	1.00	32.66	C
ATOM	3299	CG	GLN	487	43.092	37.979	7.485	1.00	37.50	C
ATOM	3300	CD	GLN	487	43.966	39.252	7.469	1.00	40.54	C
ATOM	3301	OE1	GLN	487	43.441	40.346	7.292	1.00	40.45	C
ATOM	3302	NE2	GLN	487	45.305	39.206	7.549	1.00	38.19	C
ATOM	3303	HE21	GLN	487	45.755	40.057	7.452	1.00	0.00	C2
ATOM	3304	HE22	GLN	487	45.736	38.340	7.702	1.00	0.00	C2
ATOM	3305	C	GLN	487	44.791	36.455	5.207	1.00	28.53	C
ATOM	3306	O	GLN	487	45.774	36.542	5.964	1.00	28.72	C
ATOM	3307	N	GLY	488	44.550	35.363	4.454	1.00	28.32	C
ATOM	3308	H	GLY	488	43.799	35.400	3.824	1.00	0.00	C2
ATOM	3309	CA	GLY	488	45.291	34.120	4.557	1.00	26.04	C
ATOM	3310	C	GLY	488	46.660	34.264	4.033	1.00	25.75	C2

FIG. 5UU.

```
ATOM 3311 O   GLY 488  47.660 33.946  4.712 1.00 25.86    C2
ATOM 3312 N   LEU 489  46.655 34.798  2.818 1.00 25.05    C2
ATOM 3313 H   LEU 489  45.798 35.062  2.416 1.00  0.00    C2
ATOM 3314 CA  LEU 489  47.911 34.990  2.099 1.00 25.63    C2
ATOM 3315 CB  LEU 489  47.708 35.570  0.725 1.00 27.66    C2
ATOM 3316 CG  LEU 489  46.761 34.755 -0.189 1.00 30.83    C2
ATOM 3317 CD1 LEU 489  46.373 35.506 -1.471 1.00 30.43    C2
ATOM 3318 CD2 LEU 489  47.472 33.454 -0.502 1.00 32.62    C2
ATOM 3319 C   LEU 489  48.783 35.936  2.853 1.00 25.28    C2
ATOM 3320 O   LEU 489  49.973 35.705  2.914 1.00 27.37    C2
ATOM 3321 N   LEU 490  48.237 36.935  3.534 1.00 25.79    C2
ATOM 3322 H   LEU 490  47.267 37.079  3.515 1.00  0.00    C2
ATOM 3323 CA  LEU 490  49.072 37.868  4.220 1.00 25.96    C2
ATOM 3324 CB  LEU 490  48.274 39.139  4.567 1.00 27.96    C2
ATOM 3325 CG  LEU 490  47.823 40.131  3.474 1.00 27.89    C2
ATOM 3326 CD1 LEU 490  46.772 41.019  4.123 1.00 28.03    C2
ATOM 3327 CD2 LEU 490  48.988 40.942  2.899 1.00 28.15    C2
ATOM 3328 C   LEU 490  49.619 37.243  5.459 1.00 27.33    C2
ATOM 3329 O   LEU 490  50.740 37.528  5.865 1.00 26.73    C2
ATOM 3330 N   GLN 491  48.883 36.370  6.111 1.00 29.88    C2
ATOM 3331 H   GLN 491  47.984 36.127  5.799 1.00  0.00    C2
ATOM 3332 CA  GLN 491  49.430 35.809  7.314 1.00 33.01    C2
ATOM 3333 CB  GLN 491  48.305 35.113  8.027 1.00 38.68    C2
ATOM 3334 CG  GLN 491  47.856 35.963  9.197 1.00 46.07    C2
ATOM 3335 CD  GLN 491  46.348 36.262  9.278 1.00 50.83    C2
ATOM 3336 OE1 GLN 491  45.965 37.436  9.402 1.00 51.92    C2
ATOM 3337 NE2 GLN 491  45.425 35.294  9.278 1.00 51.67    C2
ATOM 3338 HE21 GLN 491 45.723 34.353  9.288 1.00  0.00    C2
ATOM 3339 HE22 GLN 491 44.489 35.560  9.286 1.00  0.00    C2
ATOM 3340 C   GLN 491  50.582 34.867  6.986 1.00 33.58    C2
ATOM 3341 O   GLN 491  51.582 34.828  7.715 1.00 34.65    C2
ATOM 3342 N   ALA 492  50.482 34.191  5.824 1.00 34.15    C2
ATOM 3343 H   ALA 492  49.701 34.382  5.264 1.00  0.00    C2
ATOM 3344 CA  ALA 492  51.416 33.177  5.321 1.00 33.64    C2
ATOM 3345 CB  ALA 492  50.818 32.500  4.081 1.00 31.67    C2
ATOM 3346 C   ALA 492  52.802 33.678  4.959 1.00 34.79    C2

ATOM 3347 O   ALA 492  53.789 32.943  4.879 1.00 36.03    C2
ATOM 3348 N   LEU 493  52.885 34.981  4.728 1.00 35.94    C2
ATOM 3349 H   LEU 493  52.060 35.510  4.721 1.00  0.00    C2
ATOM 3350 CA  LEU 493  54.139 35.634  4.426 1.00 34.86    C2
ATOM 3351 CB  LEU 493  53.898 36.990  3.747 1.00 31.36    C2
ATOM 3352 CG  LEU 493  53.127 37.065  2.443 1.00 28.27    C2
ATOM 3353 CD1 LEU 493  52.715 38.495  2.214 1.00 31.74    C2
ATOM 3354 CD2 LEU 493  53.977 36.608  1.285 1.00 28.79    C2
ATOM 3355 C   LEU 493  54.879 35.843  5.721 1.00 36.15    C2
ATOM 3356 O   LEU 493  55.985 36.374  5.694 1.00 36.70    C2
ATOM 3357 N   GLU 494  54.300 35.497  6.855 1.00 38.35    C2
ATOM 3358 H   GLU 494  53.395 35.130  6.836 1.00  0.00    C2
ATOM 3359 CA  GLU 494  54.910 35.648  8.157 1.00 43.14    C2
ATOM 3360 CB  GLU 494  55.621 34.340  8.545 1.00 46.61    C2
ATOM 3361 CG  GLU 494  54.711 33.471  9.419 1.00 53.71    C2
ATOM 3362 CD  GLU 494  54.195 32.160  8.785 1.00 60.27    C2
ATOM 3363 OE1 GLU 494  53.146 31.653  9.230 1.00 63.52    C2
ATOM 3364 OE2 GLU 494  54.839 31.630  7.862 1.00 62.76    C2
ATOM 3365 C   GLU 494  55.865 36.825  8.343 1.00 44.32    C2
ATOM 3366 O   GLU 494  57.055 36.678  8.610 1.00 46.91    C2
ATOM 3367 N   GLY 495  55.358 38.046  8.114 1.00 44.32    C2
ATOM 3368 H   GLY 495  54.450 38.112  7.753 1.00  0.00    C2
ATOM 3369 CA  GLY 495  56.104 39.272  8.368 1.00 42.36    C2
ATOM 3370 C   GLY 495  57.015 39.695  7.238 1.00 42.33    C2
ATOM 3371 O   GLY 495  57.397 40.866  7.220 1.00 42.42    C2
ATOM 3372 N   ILE 496  57.310 38.802  6.279 1.00 41.04    C2
ATOM 3373 H   ILE 496  56.927 37.906  6.374 1.00  0.00    C2
ATOM 3374 CA  ILE 496  58.259 38.993  5.192 1.00 41.15    C2
ATOM 3375 CB  ILE 496  57.929 40.216  4.253 1.00 38.60    C2
ATOM 3376 CG2 ILE 496  59.077 40.437  3.248 1.00 37.62    C2
ATOM 3377 CG1 ILE 496  56.662 39.964  3.480 1.00 36.39    C2
ATOM 3378 CD  ILE 496  56.314 41.071  2.470 1.00 35.27    C2
ATOM 3379 C   ILE 496  59.672 39.203  5.749 1.00 42.91    C2
ATOM 3380 O   ILE 496  60.541 38.396  5.448 1.00 44.22    C2
ATOM 3381 N   SER 497  59.998 40.228  6.533 1.00 44.31    C2
ATOM 3382 H   SER 497  59.297 40.852  6.827 1.00  0.00    C2
```

FIG.5VV

```
ATOM 3383 CA  SER 497  61.346 40.501  6.992 1.00 44.86  C2
ATOM 3384 CB  SER 497  62.204 41.254  5.938 1.00 44.13  C2
ATOM 3385 OG  SER 497  62.181 42.673  6.033 1.00 40.74  C2
ATOM 3386 HG  SER 497  62.531 42.964  5.170 1.00  0.00  C2
ATOM 3387 C   SER 497  61.164 41.413  8.185 1.00 45.85  C2
ATOM 3388 O   SER 497  60.132 42.110  8.288 1.00 47.55  C2
ATOM 3389 N   PRO 498  62.164 41.490  9.071 1.00 44.96  C2
ATOM 3390 CD  PRO 498  63.338 40.621  9.126 1.00 42.33  C2
ATOM 3391 CA  PRO 498  62.086 42.327 10.250 1.00 44.88  C2
ATOM 3392 CB  PRO 498  63.431 42.038 10.885 1.00 45.13  C2
ATOM 3393 CG  PRO 498  63.629 40.581 10.603 1.00 42.00  C2
ATOM 3394 C   PRO 498  61.760 43.799  9.983 1.00 45.22  C2
ATOM 3395 O   PRO 498  61.215 44.446 10.869 1.00 45.24  C2
ATOM 3396 N   GLU 499  62.017 44.314  8.777 1.00 46.16  C2
ATOM 3397 H   GLU 499  62.362 43.716  8.081 1.00  0.00  C2
ATOM 3398 CA  GLU 499  61.731 45.699  8.391 1.00 48.06  C2
ATOM 3399 CB  GLU 499  62.498 46.193  7.155 1.00 52.19  C2
ATOM 3400 CG  GLU 499  64.001 46.187  7.100 1.00 57.51  C2
ATOM 3401 CD  GLU 499  64.544 44.777  7.076 1.00 60.61  C2
ATOM 3402 OE1 GLU 499  64.755 44.231  8.162 1.00 62.96  C2
ATOM 3403 OE2 GLU 499  64.739 44.234  5.984 1.00 62.79  C2
ATOM 3404 C   GLU 499  60.269 45.896  7.981 1.00 46.94  C2
ATOM 3405 O   GLU 499  59.600 46.895  8.272 1.00 48.15  C2
ATOM 3406 N   LEU 500  59.806 44.934  7.193 1.00 44.38  C2
ATOM 3407 H   LEU 500  60.351 44.137  7.027 1.00  0.00  C2
ATOM 3408 CA  LEU 500  58.491 44.997  6.651 1.00 41.08  C2
ATOM 3409 CB  LEU 500  58.519 44.197  5.445 1.00 41.37  C2
ATOM 3410 CG  LEU 500  59.303 44.862  4.351 1.00 42.70  C2
ATOM 3411 CD1 LEU 500  59.776 43.828  3.351 1.00 43.98  C2
ATOM 3412 CD2 LEU 500  58.427 45.874  3.671 1.00 45.04  C2
ATOM 3413 C   LEU 500  57.455 44.521  7.628 1.00 40.59  C2
ATOM 3414 O   LEU 500  56.274 44.835  7.463 1.00 40.69  C2
ATOM 3415 N   GLY 501  57.866 43.835  8.685 1.00 39.37  C2
ATOM 3416 H   GLY 501  58.808 43.579  8.730 1.00  0.00  C2
ATOM 3417 CA  GLY 501  56.974 43.386  9.734 1.00 39.59  C2
ATOM 3418 C   GLY 501  55.816 44.324 10.092 1.00 39.66  C2

ATOM 3419 O   GLY 501  54.661 44.034  9.777 1.00 40.66  C2
ATOM 3420 N   PRO 502  55.986 45.462 10.742 1.00 39.90  C2
ATOM 3421 CD  PRO 502  57.227 45.908 11.335 1.00 41.18  C2
ATOM 3422 CA  PRO 502  54.912 46.387 11.045 1.00 38.67  C2
ATOM 3423 CB  PRO 502  55.594 47.494 11.791 1.00 39.23  C2
ATOM 3424 CG  PRO 502  56.989 47.405 11.221 1.00 41.36  C2
ATOM 3425 C   PRO 502  54.158 46.849  9.817 1.00 37.54  C2
ATOM 3426 O   PRO 502  52.966 47.139  9.961 1.00 38.36  C2
ATOM 3427 N   THR 503  54.728 46.887  8.609 1.00 35.13  C2
ATOM 3428 H   THR 503  55.663 46.638  8.449 1.00  0.00  C2
ATOM 3429 CA  THR 503  53.940 47.283  7.462 1.00 35.09  C2
ATOM 3430 CB  THR 503  54.832 47.376  6.245 1.00 34.48  C2
ATOM 3431 OG1 THR 503  56.025 48.018  6.668 1.00 38.23  C2
ATOM 3432 HG1 THR 503  55.857 48.946  6.845 1.00  0.00  C2
ATOM 3433 CG2 THR 503  54.197 48.162  5.126 1.00 35.56  C2
ATOM 3434 C   THR 503  52.836 46.252  7.215 1.00 35.37  C2
ATOM 3435 O   THR 503  51.671 46.552  6.915 1.00 37.11  C2
ATOM 3436 N   LEU 504  53.218 44.996  7.380 1.00 34.02  C2
ATOM 3437 H   LEU 504  54.146 44.799  7.647 1.00  0.00  C2
ATOM 3438 CA  LEU 504  52.301 43.912  7.173 1.00 32.50  C2
ATOM 3439 CB  LEU 504  53.127 42.650  7.002 1.00 34.78  C2
ATOM 3440 CG  LEU 504  53.464 42.256  5.601 1.00 34.07  C2
ATOM 3441 CD1 LEU 504  54.163 40.977  5.667 1.00 37.97  C2
ATOM 3442 CD2 LEU 504  52.254 41.865  4.809 1.00 37.34  C2
ATOM 3443 C   LEU 504  51.324 43.821  8.328 1.00 29.54  C2
ATOM 3444 O   LEU 504  50.141 43.562  8.078 1.00 30.40  C2
ATOM 3445 N   ASP 505  51.736 44.106  9.551 1.00 26.09  C2
ATOM 3446 H   ASP 505  52.689 44.269  9.699 1.00  0.00  C2
ATOM 3447 CA  ASP 505  50.798 44.084 10.643 1.00 27.88  C2
ATOM 3448 CB  ASP 505  51.446 44.345 11.926 1.00 29.86  C2
ATOM 3449 CG  ASP 505  52.500 43.312 12.239 1.00 34.64  C2
ATOM 3450 OD1 ASP 505  52.663 42.298 11.534 1.00 41.04  C2
ATOM 3451 OD2 ASP 505  53.179 43.542 13.224 1.00 37.40  C2
ATOM 3452 C   ASP 505  49.661 45.060 10.568 1.00 28.61  C2
ATOM 3453 O   ASP 505  48.566 44.739 11.039 1.00 30.30  C2
ATOM 3454 N   THR 506  49.894 46.242 10.002 1.00 28.29  C2
```

FIG.5WW

```
ATOM 3455 H   THR 506  50.823 46.493  9.804 1.00  0.00 H
ATOM 3456 CA  THR 506  48.860 47.225  9.731 1.00 25.74 C
ATOM 3457 CB  THR 506  49.497 48.556  9.336 1.00 26.14 C
ATOM 3458 OG1 THR 506  49.944 49.099 10.588 1.00 31.63 O
ATOM 3459 HG1 THR 506  49.243 49.072 11.246 1.00  0.00 H
ATOM 3460 CG2 THR 506  48.594 49.517  8.619 1.00 24.46 C
ATOM 3461 C   THR 506  48.022 46.735  8.615 1.00 24.00 C
ATOM 3462 O   THR 506  46.817 46.864  8.719 1.00 25.85 O
ATOM 3463 N   LEU 507  48.554 46.196  7.525 1.00 23.51 N
ATOM 3464 H   LEU 507  49.527 46.073  7.453 1.00  0.00 H
ATOM 3465 CA  LEU 507  47.682 45.770  6.434 1.00 23.85 C
ATOM 3466 CB  LEU 507  48.574 45.408  5.196 1.00 23.33 C
ATOM 3467 CG  LEU 507  48.010 44.919  3.858 1.00 20.85 C
ATOM 3468 CD1 LEU 507  46.771 45.650  3.455 1.00 24.13 C
ATOM 3469 CD2 LEU 507  49.074 45.055  2.842 1.00 20.13 C
ATOM 3470 C   LEU 507  46.766 44.640  6.880 1.00 24.09 C
ATOM 3471 O   LEU 507  45.600 44.764  6.541 1.00 25.80 O
ATOM 3472 N   GLN 508  47.152 43.618  7.661 1.00 24.01 N
ATOM 3473 H   GLN 508  48.112 43.555  7.866 1.00  0.00 H
ATOM 3474 CA  GLN 508  46.228 42.625  8.214 1.00 23.71 C
ATOM 3475 CB  GLN 508  46.961 41.627  9.036 1.00 23.83 C
ATOM 3476 CG  GLN 508  47.937 40.899  8.173 1.00 31.64 C
ATOM 3477 CD  GLN 508  48.842 40.080  9.054 1.00 34.00 C
ATOM 3478 OE1 GLN 508  50.031 40.346  9.161 1.00 38.32 O
ATOM 3479 NE2 GLN 508  48.321 39.090  9.748 1.00 36.30 N
ATOM 3480 HE21 GLN 508 47.373 38.880  9.639 1.00  0.00 H
ATOM 3481 HE22 GLN 508 48.891 38.636 10.406 1.00  0.00 H
ATOM 3482 C   GLN 508  45.105 43.123  9.111 1.00 24.24 C
ATOM 3483 O   GLN 508  43.978 42.650  9.014 1.00 24.06 O
ATOM 3484 N   LEU 509  45.375 44.019 10.090 1.00 26.07 N
ATOM 3485 H   LEU 509  46.316 44.262 10.222 1.00  0.00 H
ATOM 3486 CA  LEU 509  44.378 44.640 10.977 1.00 25.71 C
ATOM 3487 CB  LEU 509  44.993 45.555 12.031 1.00 25.60 C
ATOM 3488 CG  LEU 509  45.838 44.757 13.042 1.00 29.00 C
ATOM 3489 CD1 LEU 509  46.658 45.705 13.886 1.00 28.93 C
ATOM 3490 CD2 LEU 509  44.950 43.919 13.937 1.00 27.94 C
ATOM 3491 C   LEU 509  43.465 45.471 10.130 1.00 25.17 C
ATOM 3492 O   LEU 509  42.274 45.411 10.408 1.00 27.22 O
ATOM 3493 N   ASP 510  43.899 46.208  9.101 1.00 23.77 N
ATOM 3494 H   ASP 510  44.865 46.277  8.930 1.00  0.00 H
ATOM 3495 CA  ASP 510  42.955 46.898  8.240 1.00 22.66 C
ATOM 3496 CB  ASP 510  43.652 47.829  7.306 1.00 25.21 C
ATOM 3497 CG  ASP 510  44.316 48.966  8.068 1.00 33.01 C
ATOM 3498 OD1 ASP 510  45.178 49.621  7.477 1.00 34.28 O
ATOM 3499 OD2 ASP 510  43.988 49.209  9.250 1.00 34.44 O
ATOM 3500 C   ASP 510  42.104 45.980  7.398 1.00 23.72 C
ATOM 3501 O   ASP 510  40.897 46.220  7.387 1.00 24.80 O
ATOM 3502 N   VAL 511  42.632 44.984  6.659 1.00 22.38 N
ATOM 3503 H   VAL 511  43.611 44.900  6.620 1.00  0.00 H
ATOM 3504 CA  VAL 511  41.823 44.010  5.961 1.00 21.89 C
ATOM 3505 CB  VAL 511  42.752 42.924  5.366 1.00 22.71 C
ATOM 3506 CG1 VAL 511  41.954 41.756  4.792 1.00 20.43 C
ATOM 3507 CG2 VAL 511  43.529 43.524  4.210 1.00 16.19 C
ATOM 3508 C   VAL 511  40.827 43.403  6.960 1.00 21.92 C
ATOM 3509 O   VAL 511  39.625 43.447  6.719 1.00 23.46 O
ATOM 3510 N   ALA 512  41.258 43.017  8.163 1.00 20.49 N
ATOM 3511 H   ALA 512  42.216 43.063  8.361 1.00  0.00 H
ATOM 3512 CA  ALA 512  40.388 42.357  9.108 1.00 20.83 C
ATOM 3513 CB  ALA 512  41.103 41.974 10.344 1.00 17.89 C
ATOM 3514 C   ALA 512  39.250 43.205  9.550 1.00 23.89 C
ATOM 3515 O   ALA 512  38.201 42.668  9.874 1.00 24.61 O
ATOM 3516 N   ASP 513  39.417 44.539  9.544 1.00 25.96 N
ATOM 3517 H   ASP 513  40.300 44.888  9.291 1.00  0.00 H
ATOM 3518 CA  ASP 513  38.374 45.471  9.947 1.00 25.37 C
ATOM 3519 CB  ASP 513  38.958 46.787 10.373 1.00 26.88 C
ATOM 3520 CG  ASP 513  39.682 46.679 11.712 1.00 32.35 C
ATOM 3521 OD1 ASP 513  40.371 47.644 12.058 1.00 35.06 O
ATOM 3522 OD2 ASP 513  39.580 45.646 12.390 1.00 34.10 O
ATOM 3523 C   ASP 513  37.392 45.730  8.846 1.00 24.95 C
ATOM 3524 O   ASP 513  36.185 45.868  9.090 1.00 26.92 O
ATOM 3525 N   PHE 514  37.867 45.739  7.634 1.00 22.88 N
ATOM 3526 H   PHE 514  38.829 45.614  7.475 1.00  0.00 H
```

FIG.5XX

```
ATOM 3527 CA  PHE 514  36.974 45.922  6.530 1.00 24.09 C2
ATOM 3528 CB  PHE 514  37.812 46.061  5.266 1.00 18.11 C2
ATOM 3529 CG  PHE 514  36.956 46.470  4.072 1.00 17.86 C2
ATOM 3530 CD1 PHE 514  35.715 47.089  4.245 1.00 15.18 C2
ATOM 3531 CD2 PHE 514  37.440 46.197  2.804 1.00 13.77 C2
ATOM 3532 CE1 PHE 514  34.983 47.419  3.130 1.00 14.53 C2
ATOM 3533 CE2 PHE 514  36.693 46.539  1.705 1.00 12.10 C2
ATOM 3534 CZ  PHE 514  35.468 47.146  1.868 1.00 10.68 C2
ATOM 3535 C   PHE 514  36.026 44.703  6.450 1.00 29.23 C2
ATOM 3536 O   PHE 514  34.788 44.828  6.350 1.00 29.80 C2
ATOM 3537 N   ALA 515  36.604 43.490  6.531 1.00 31.15 C2
ATOM 3538 H   ALA 515  37.581 43.450  6.639 1.00  0.00 C2
ATOM 3539 CA  ALA 515  35.839 42.260  6.416 1.00 32.36 C2
ATOM 3540 CB  ALA 515  36.851 41.126  6.402 1.00 32.35 C2
ATOM 3541 C   ALA 515  34.801 42.089  7.535 1.00 32.39 C2
ATOM 3542 O   ALA 515  33.676 41.609  7.331 1.00 32.63 C2
ATOM 3543 N   THR 516  35.164 42.457  8.735 1.00 33.01 C2
ATOM 3544 H   THR 516  36.117 42.578  8.935 1.00  0.00 C2
ATOM 3545 CA  THR 516  34.231 42.566  9.821 1.00 35.18 C2
ATOM 3546 CB  THR 516  35.016 43.018 10.988 1.00 35.40 C2
ATOM 3547 OG1 THR 516  35.685 41.818 11.336 1.00 42.65 C2
ATOM 3548 HG1 THR 516  36.505 41.713 10.816 1.00  0.00 C2
ATOM 3549 CG2 THR 516  34.262 43.672 12.097 1.00 35.56 C2
ATOM 3550 C   THR 516  33.140 43.554  9.482 1.00 37.62 C2
ATOM 3551 O   THR 516  32.005 43.315  9.857 1.00 40.37 C2
ATOM 3552 N   THR 517  33.387 44.666  8.802 1.00 38.61 C2
ATOM 3553 H   THR 517  34.291 44.850  8.469 1.00  0.00 C2
ATOM 3554 CA  THR 517  32.359 45.641  8.512 1.00 38.92 C2
ATOM 3555 CB  THR 517  33.123 46.903  7.962 1.00 40.46 C2
ATOM 3556 OG1 THR 517  33.832 47.429  9.103 1.00 43.22 C2
ATOM 3557 HG1 THR 517  34.536 46.815  9.335 1.00  0.00 C2
ATOM 3558 CG2 THR 517  32.232 47.926  7.253 1.00 39.90 C2
ATOM 3559 C   THR 517  31.343 45.012  7.551 1.00 38.30 C2
ATOM 3560 O   THR 517  30.137 45.125  7.811 1.00 38.69 C2
ATOM 3561 N   ILE 518  31.790 44.344  6.466 1.00 37.54 C2
ATOM 3562 H   ILE 518  32.756 44.386  6.297 1.00  0.00 C2

ATOM 3563 CA  ILE 518  30.923 43.646  5.510 1.00 36.10 C2
ATOM 3564 CB  ILE 518  31.699 42.912  4.439 1.00 33.81 C2
ATOM 3565 CG2 ILE 518  30.703 42.202  3.555 1.00 33.46 C2
ATOM 3566 CG1 ILE 518  32.623 43.842  3.699 1.00 32.91 C2
ATOM 3567 CD  ILE 518  32.019 44.700  2.596 1.00 34.89 C2
ATOM 3568 C   ILE 518  30.172 42.591  6.317 1.00 38.63 C2
ATOM 3569 O   ILE 518  28.938 42.545  6.205 1.00 39.93 C2
ATOM 3570 N   TRP 519  30.842 41.785  7.179 1.00 38.64 C2
ATOM 3571 H   TRP 519  31.785 41.959  7.361 1.00  0.00 C2
ATOM 3572 CA  TRP 519  30.144 40.784  7.945 1.00 38.15 C2
ATOM 3573 CB  TRP 519  31.124 40.083  8.780 1.00 38.52 C2
ATOM 3574 CG  TRP 519  30.493 38.793  9.255 1.00 42.26 C2
ATOM 3575 CD2 TRP 519  29.880 38.578 10.473 1.00 41.70 C2
ATOM 3576 CE2 TRP 519  29.437 37.278 10.335 1.00 41.69 C2
ATOM 3577 CE3 TRP 519  29.648 39.282 11.629 1.00 42.26 C2
ATOM 3578 CD1 TRP 519  30.448 37.695  8.419 1.00 42.92 C2
ATOM 3579 NE1 TRP 519  29.788 36.793  9.115 1.00 44.19 C2
ATOM 3580 HE1 TRP 519  29.485 35.935  8.741 1.00  0.00 C2
ATOM 3581 CZ2 TRP 519  28.753 36.671 11.360 1.00 41.91 C2
ATOM 3582 CZ3 TRP 519  28.964 38.666 12.652 1.00 41.77 C2
ATOM 3583 CH2 TRP 519  28.522 37.375 12.515 1.00 41.05 C2
ATOM 3584 C   TRP 519  29.027 41.368  8.815 1.00 39.33 C2
ATOM 3585 O   TRP 519  27.888 40.919  8.726 1.00 38.28 C2
ATOM 3586 N   GLN 520  29.264 42.375  9.650 1.00 41.86 C2
ATOM 3587 H   GLN 520  30.180 42.717  9.700 1.00  0.00 C2
ATOM 3588 CA  GLN 520  28.240 43.016 10.464 1.00 44.63 C2
ATOM 3589 CB  GLN 520  28.691 44.198 11.239 1.00 47.03 C2
ATOM 3590 CG  GLN 520  29.602 43.808 12.360 1.00 54.78 C2
ATOM 3591 CD  GLN 520  29.910 45.009 13.243 1.00 60.14 C2
ATOM 3592 OE1 GLN 520  28.988 45.566 13.854 1.00 61.62 C2
ATOM 3593 NE2 GLN 520  31.172 45.456 13.371 1.00 60.46 C2
ATOM 3594 HE21 GLN 520 31.289 46.260 13.910 1.00  0.00 C2
ATOM 3595 HE22 GLN 520 31.895 44.966 12.932 1.00  0.00 C2
ATOM 3596 C   GLN 520  27.141 43.577  9.621 1.00 46.28 C2
ATOM 3597 O   GLN 520  26.001 43.474 10.059 1.00 48.62 C2
ATOM 3598 N   GLN 521  27.362 44.145  8.442 1.00 46.99 C2
```

FIG.5YY

```
ATOM 3599 H    GLN 521 28.272 44.257  8.092 1.00  0.00 C2
ATOM 3600 CA   GLN 521 26.226 44.638  7.716 1.00 49.02 C2
ATOM 3601 CB   GLN 521 26.632 45.553  6.566 1.00 50.06 C2
ATOM 3602 CG   GLN 521 25.456 46.226  5.790 1.00 50.87 C2
ATOM 3603 CD   GLN 521 24.616 47.278  6.534 1.00 51.82 C2
ATOM 3604 OE1  GLN 521 24.864 47.694  7.671 1.00 52.47 C2
ATOM 3605 NE2  GLN 521 23.577 47.776  5.888 1.00 50.36 C2
ATOM 3606 HE21 GLN 521 23.392 47.455  4.987 1.00  0.00 C2
ATOM 3607 HE22 GLN 521 23.044 48.424  6.390 1.00  0.00 C2
ATOM 3608 C    GLN 521 25.454 43.446  7.155 1.00 50.15 C2
ATOM 3609 O    GLN 521 24.214 43.514  7.177 1.00 51.82 C2
ATOM 3610 N    MET 522 26.057 42.348  6.668 1.00 49.18 C2
ATOM 3611 H    MET 522 27.038 42.291  6.688 1.00  0.00 C2
ATOM 3612 CA   MET 522 25.280 41.227  6.171 1.00 48.22 C2
ATOM 3613 CB   MET 522 26.185 40.167  5.607 1.00 46.36 C2
ATOM 3614 CG   MET 522 26.942 40.661  4.412 1.00 44.32 C2
ATOM 3615 SD   MET 522 27.855 39.435  3.426 1.00 48.35 C2
ATOM 3616 CE   MET 522 28.795 38.447  4.565 1.00 42.80 C2
ATOM 3617 C    MET 522 24.453 40.642  7.316 1.00 50.14 C2
ATOM 3618 O    MET 522 23.380 40.124  7.038 1.00 50.60 C2
ATOM 3619 N    GLU 523 24.848 40.722  8.596 1.00 51.91 C2
ATOM 3620 H    GLU 523 25.766 41.031  8.769 1.00  0.00 C2
ATOM 3621 CA   GLU 523 24.027 40.313  9.718 1.00 54.53 C2
ATOM 3622 CB   GLU 523 24.654 40.486 11.081 1.00 54.60 C2
ATOM 3623 CG   GLU 523 25.732 39.525 11.398 1.00 57.05 C2
ATOM 3624 CD   GLU 523 25.386 38.150 10.888 1.00 61.72 C2
ATOM 3625 OE1  GLU 523 24.515 37.487 11.477 1.00 64.60 C2
ATOM 3626 OE2  GLU 523 25.979 37.773  9.872 1.00 63.19 C2
ATOM 3627 C    GLU 523 22.773 41.116  9.836 1.00 58.29 C2
ATOM 3628 O    GLU 523 21.688 40.538  9.850 1.00 59.32 C2
ATOM 3629 N    ALA 524 22.920 42.432  9.992 1.00 61.41 C2
ATOM 3630 H    ALA 524 23.834 42.798 10.024 1.00  0.00 C2
ATOM 3631 CA   ALA 524 21.815 43.360 10.076 1.00 63.58 C2
ATOM 3632 CB   ALA 524 22.382 44.768  9.992 1.00 64.11 C2
ATOM 3633 C    ALA 524 20.818 43.109  8.946 1.00 64.79 C2
ATOM 3634 O    ALA 524 19.655 42.824  9.206 1.00 65.69 C2

ATOM 3635 N    ALA 525 21.251 43.083  7.693 1.00 66.44 C2
ATOM 3636 H    ALA 525 22.196 43.283  7.516 1.00  0.00 C2
ATOM 3637 CA   ALA 525 20.371 42.789  6.574 1.00 68.58 C2
ATOM 3638 CB   ALA 525 21.117 43.044  5.288 1.00 67.42 C2
ATOM 3639 C    ALA 525 19.841 41.356  6.558 1.00 71.11 C2
ATOM 3640 O    ALA 525 19.116 40.946  5.651 1.00 71.65 C2
ATOM 3641 N    GLY 526 20.257 40.510  7.498 1.00 74.20 C2
ATOM 3642 H    GLY 526 21.019 40.780  8.043 1.00  0.00 C2
ATOM 3643 CA   GLY 526 19.728 39.157  7.653 1.00 76.30 C2
ATOM 3644 C    GLY 526 20.430 38.085  6.842 1.00 78.19 C2
ATOM 3645 O    GLY 526 20.174 36.910  7.094 1.00 79.05 C2
ATOM 3646 N    MET 527 21.388 38.433  5.970 1.00 80.23 C2
ATOM 3647 H    MET 527 21.759 39.337  6.075 1.00  0.00 C2
ATOM 3648 CA   MET 527 22.055 37.489  5.063 1.00 81.73 C2
ATOM 3649 CB   MET 527 22.771 38.256  3.928 1.00 81.72 C2
ATOM 3650 CG   MET 527 22.385 39.719  3.720 1.00 83.52 C2
ATOM 3651 SD   MET 527 23.364 40.523  2.436 1.00 87.64 C2
ATOM 3652 CE   MET 527 22.600 42.117  2.409 1.00 84.47 C2
ATOM 3653 C    MET 527 23.078 36.584  5.780 1.00 82.64 C2
ATOM 3654 OT1  MET 527 22.974 35.357  5.624 1.00 83.38 C2
ATOM 3655 OT2  MET 527 23.949 37.104  6.500 1.00 82.90 C2
ATOM 3656 CB   MET 538 47.224 28.531  2.401 1.00 77.43 C2
ATOM 3657 CG   MET 538 47.397 30.041  2.427 1.00 77.15 C2
ATOM 3658 SD   MET 538 46.205 30.708  3.604 1.00 79.03 C2
ATOM 3659 CE   MET 538 44.850 31.067  2.515 1.00 77.20 C2
ATOM 3660 C    MET 538 48.549 27.839  0.386 1.00 75.32 C2
ATOM 3661 O    MET 538 49.130 26.745  0.405 1.00 77.11 C2
ATOM 3662 HT1  MET 538 47.563 26.068  1.449 1.00  0.00 C2
ATOM 3663 HT2  MET 538 46.638 26.204  0.075 1.00  0.00 C2
ATOM 3664 N    MET 538 46.724 26.552  1.050 1.00 77.52 C2
ATOM 3665 HT3  MET 538 45.873 26.401  1.617 1.00  0.00 C2
ATOM 3666 CA   MET 538 47.153 27.940  0.995 1.00 76.57 C2
ATOM 3667 N    PRO 539 49.089 28.870 -0.224 1.00 72.65 C2
ATOM 3668 CD   PRO 539 48.346 29.821 -1.046 1.00 72.26 C2
ATOM 3669 CA   PRO 539 50.526 29.020 -0.349 1.00 70.34 C2
ATOM 3670 CB   PRO 539 50.677 30.365 -1.006 1.00 71.39 C2
```

FIG.5ZZ.

```
ATOM  3671 CG  PRO 539  49.437 30.503 -1.837 1.00 71.52 C
ATOM  3672 C   PRO 539  51.250 28.931  0.991 1.00 67.83 C
ATOM  3673 O   PRO 539  50.666 29.294  2.029 1.00 68.05 C
ATOM  3674 N   ALA 540  52.484 28.417  0.961 1.00 64.48 C
ATOM  3675 H   ALA 540  52.858 28.098  0.111 1.00  0.00 C
ATOM  3676 CA  ALA 540  53.389 28.498  2.112 1.00 61.83 C
ATOM  3677 CB  ALA 540  54.004 27.200  2.619 1.00 63.57 C
ATOM  3678 C   ALA 540  54.559 29.212  1.496 1.00 58.74 C
ATOM  3679 O   ALA 540  54.835 29.036  0.301 1.00 58.30 C
ATOM  3680 N   PHE 541  55.256 30.008  2.292 1.00 55.25 C
ATOM  3681 H   PHE 541  55.093 30.068  3.257 1.00  0.00 C
ATOM  3682 CA  PHE 541  56.299 30.814  1.702 1.00 51.38 C
ATOM  3683 CB  PHE 541  55.964 32.306  1.942 1.00 48.80 C
ATOM  3684 CG  PHE 541  54.789 32.703  1.058 1.00 45.77 C
ATOM  3685 CD1 PHE 541  54.992 32.939 -0.279 1.00 44.20 C
ATOM  3686 CD2 PHE 541  53.507 32.747  1.582 1.00 44.76 C
ATOM  3687 CE1 PHE 541  53.901 33.207 -1.074 1.00 43.98 C
ATOM  3688 CE2 PHE 541  52.428 33.018  0.769 1.00 42.86 C
ATOM  3689 CZ  PHE 541  52.625 33.247 -0.563 1.00 42.52 C
ATOM  3690 C   PHE 541  57.586 30.364  2.333 1.00 49.80 C
ATOM  3691 O   PHE 541  58.002 30.807  3.395 1.00 49.55 C
ATOM  3692 N   ALA 542  58.172 29.442  1.562 1.00 48.21 C
ATOM  3693 H   ALA 542  57.825 29.298  0.656 1.00  0.00 C
ATOM  3694 CA  ALA 542  59.326 28.711  1.968 1.00 45.37 C
ATOM  3695 CB  ALA 542  59.700 27.749  0.898 1.00 45.21 C
ATOM  3696 C   ALA 542  60.510 29.567  2.266 1.00 44.87 C
ATOM  3697 O   ALA 542  61.001 29.504  3.374 1.00 46.49 C
ATOM  3698 N   SER 543  61.013 30.408  1.395 1.00 42.63 C
ATOM  3699 H   SER 543  60.477 30.685  0.630 1.00  0.00 C
ATOM  3700 CA  SER 543  62.253 31.108  1.708 1.00 40.31 C
ATOM  3701 CB  SER 543  63.170 30.861  0.587 1.00 37.74 C
ATOM  3702 OG  SER 543  62.391 31.181 -0.554 1.00 35.74 C
ATOM  3703 HG  SER 543  61.824 30.423 -0.751 1.00  0.00 C
ATOM  3704 C   SER 543  62.087 32.613  1.896 1.00 40.88 C
ATOM  3705 O   SER 543  61.016 33.115  1.536 1.00 42.63 C
ATOM  3706 N   ALA 544  63.120 33.383  2.310 1.00 38.84 C
ATOM  3707 H   ALA 544  63.929 32.951  2.650 1.00  0.00 C
ATOM  3708 CA  ALA 544  63.035 34.836  2.345 1.00 37.31 C
ATOM  3709 CB  ALA 544  64.340 35.450  2.808 1.00 35.74 C
ATOM  3710 C   ALA 544  62.723 35.372  0.947 1.00 37.06 C
ATOM  3711 O   ALA 544  61.829 36.220  0.820 1.00 38.23 C
ATOM  3712 N   PHE 545  63.357 34.881 -0.130 1.00 35.72 C
ATOM  3713 H   PHE 545  64.131 34.298 -0.010 1.00  0.00 C
ATOM  3714 CA  PHE 545  62.992 35.268 -1.484 1.00 33.66 C
ATOM  3715 CB  PHE 545  63.738 34.534 -2.593 1.00 29.71 C
ATOM  3716 CG  PHE 545  63.140 34.742 -3.990 1.00 29.62 C
ATOM  3717 CD1 PHE 545  62.317 33.788 -4.557 1.00 29.80 C
ATOM  3718 CD2 PHE 545  63.371 35.915 -4.689 1.00 31.90 C
ATOM  3719 CE1 PHE 545  61.723 33.984 -5.795 1.00 28.61 C
ATOM  3720 CE2 PHE 545  62.777 36.113 -5.928 1.00 31.00 C
ATOM  3721 CZ  PHE 545  61.955 35.150 -6.480 1.00 31.01 C
ATOM  3722 C   PHE 545  61.543 34.900 -1.667 1.00 34.81 C
ATOM  3723 O   PHE 545  60.901 35.660 -2.389 1.00 38.88 C
ATOM  3724 N   GLN 546  60.912 33.847 -1.135 1.00 34.77 C
ATOM  3725 H   GLN 546  61.396 33.223 -0.558 1.00  0.00 C
ATOM  3726 CA  GLN 546  59.490 33.637 -1.433 1.00 33.72 C
ATOM  3727 CB  GLN 546  59.145 32.232 -1.140 1.00 34.85 C
ATOM  3728 CG  GLN 546  59.582 31.585 -2.444 1.00 42.45 C
ATOM  3729 CD  GLN 546  59.374 30.085 -2.473 1.00 46.05 C
ATOM  3730 OE1 GLN 546  59.287 29.472 -1.399 1.00 48.90 C
ATOM  3731 NE2 GLN 546  59.339 29.442 -3.644 1.00 47.20 C
ATOM  3732 HE21 GLN 546 59.476 29.948 -4.472 1.00  0.00 C
ATOM  3733 HE22 GLN 546 59.154 28.481 -3.609 1.00  0.00 C
ATOM  3734 C   GLN 546  58.504 34.541 -0.729 1.00 31.62 C
ATOM  3735 O   GLN 546  57.429 34.850 -1.233 1.00 29.88 C
ATOM  3736 N   ARG 547  58.907 34.929  0.465 1.00 31.09 C
ATOM  3737 H   ARG 547  59.750 34.566  0.811 1.00  0.00 C
ATOM  3738 CA  ARG 547  58.160 35.830  1.282 1.00 31.43 C
ATOM  3739 CB  ARG 547  58.813 35.874  2.601 1.00 31.74 C
ATOM  3740 CG  ARG 547  57.906 35.224  3.623 1.00 37.02 C
ATOM  3741 CD  ARG 547  58.344 33.858  4.076 1.00 40.56 C
ATOM  3742 NE  ARG 547  59.743 34.058  4.345 1.00 47.90 C
```

FIG. 5AAA

```
ATOM 3743 HE   ARG 547  60.389 33.924  3.620 1.00  0.00
ATOM 3744 CZ   ARG 547  60.190 34.394  5.543 1.00 49.48
ATOM 3745 NH1  ARG 547  59.361 34.522  6.593 1.00 51.97
ATOM 3746 HH11 ARG 547  58.380 34.356  6.488 1.00  0.00
ATOM 3747 HH12 ARG 547  59.731 34.763  7.491 1.00  0.00
ATOM 3748 NH2  ARG 547  61.464 34.775  5.616 1.00 48.55
ATOM 3749 HH21 ARG 547  62.025 34.803  4.788 1.00  0.00
ATOM 3750 HH22 ARG 547  61.854 35.034  6.501 1.00  0.00
ATOM 3751 C    ARG 547  58.167 37.181  0.590 1.00 32.26
ATOM 3752 O    ARG 547  57.084 37.694  0.317 1.00 34.25
ATOM 3753 N    ARG 548  59.348 37.717  0.205 1.00 31.44
ATOM 3754 H    ARG 548  60.148 37.203  0.444 1.00  0.00
ATOM 3755 CA   ARG 548  59.529 38.980 -0.555 1.00 30.01
ATOM 3756 CB   ARG 548  60.995 39.213 -0.949 1.00 25.42
ATOM 3757 CG   ARG 548  61.820 39.361  0.294 1.00 26.11
ATOM 3758 CD   ARG 548  63.280 39.158 -0.054 1.00 29.34
ATOM 3759 NE   ARG 548  64.044 39.162  1.189 1.00 32.30
ATOM 3760 HE   ARG 548  63.572 38.883  1.995 1.00  0.00
ATOM 3761 CZ   ARG 548  65.344 39.518  1.325 1.00 32.66
ATOM 3762 NH1  ARG 548  66.159 39.923  0.335 1.00 34.98
ATOM 3763 HH11 ARG 548  67.107 40.170  0.533 1.00  0.00
ATOM 3764 HH12 ARG 548  65.812 39.981 -0.600 1.00  0.00
ATOM 3765 NH2  ARG 548  65.837 39.518  2.549 1.00 32.03
ATOM 3766 HH21 ARG 548  66.788 39.783  2.708 1.00  0.00
ATOM 3767 HH22 ARG 548  65.250 39.275  3.321 1.00  0.00
ATOM 3768 C    ARG 548  58.713 38.997 -1.832 1.00 29.81
ATOM 3769 O    ARG 548  57.778 39.790 -1.968 1.00 33.03
ATOM 3770 N    ALA 549  58.979 38.102 -2.761 1.00 27.87
ATOM 3771 H    ALA 549  59.684 37.436 -2.601 1.00  0.00
ATOM 3772 CA   ALA 549  58.227 38.045 -3.984 1.00 27.18
ATOM 3773 CB   ALA 549  58.797 36.934 -4.857 1.00 28.72
ATOM 3774 C    ALA 549  56.748 37.810 -3.770 1.00 25.91
ATOM 3775 O    ALA 549  55.896 38.337 -4.468 1.00 26.03
ATOM 3776 N    GLY 550  56.421 37.074 -2.748 1.00 26.53
ATOM 3777 H    GLY 550  57.103 36.657 -2.185 1.00  0.00
ATOM 3778 CA   GLY 550  55.055 36.805 -2.457 1.00 26.08
ATOM 3779 C    GLY 550  54.410 38.098 -2.075 1.00 26.94
ATOM 3780 O    GLY 550  53.339 38.380 -2.608 1.00 26.59
ATOM 3781 N    GLY 551  55.073 38.917 -1.234 1.00 27.78
ATOM 3782 H    GLY 551  55.958 38.642 -0.925 1.00  0.00
ATOM 3783 CA   GLY 551  54.540 40.212 -0.779 1.00 26.51
ATOM 3784 C    GLY 551  54.302 41.113 -1.994 1.00 26.82
ATOM 3785 O    GLY 551  53.313 41.852 -2.065 1.00 27.82
ATOM 3786 N    VAL 552  55.154 41.013 -3.012 1.00 25.81
ATOM 3787 H    VAL 552  55.916 40.396 -2.954 1.00  0.00
ATOM 3788 CA   VAL 552  54.952 41.843 -4.176 1.00 28.39
ATOM 3789 CB   VAL 552  56.178 41.743 -5.190 1.00 26.20
ATOM 3790 CG1  VAL 552  55.917 42.391 -6.541 1.00 26.53
ATOM 3791 CG2  VAL 552  57.327 42.546 -4.594 1.00 26.44
ATOM 3792 C    VAL 552  53.650 41.406 -4.820 1.00 29.05
ATOM 3793 O    VAL 552  52.744 42.251 -4.888 1.00 31.68
ATOM 3794 N    LEU 553  53.455 40.120 -5.176 1.00 27.20
ATOM 3795 H    LEU 553  54.122 39.447 -4.908 1.00  0.00
ATOM 3796 CA   LEU 553  52.266 39.705 -5.915 1.00 23.80
ATOM 3797 CB   LEU 553  52.357 38.262 -6.363 1.00 24.86
ATOM 3798 CG   LEU 553  53.432 37.955 -7.357 1.00 23.06
ATOM 3799 CD1  LEU 553  54.073 36.623 -7.092 1.00 24.31
ATOM 3800 CD2  LEU 553  52.794 38.061 -8.703 1.00 21.87
ATOM 3801 C    LEU 553  51.012 39.825 -5.114 1.00 23.72
ATOM 3802 O    LEU 553  49.982 40.138 -5.712 1.00 24.63
ATOM 3803 N    VAL 554  50.962 39.580 -3.803 1.00 24.37
ATOM 3804 H    VAL 554  51.774 39.350 -3.295 1.00  0.00
ATOM 3805 CA   VAL 554  49.660 39.691 -3.180 1.00 26.36
ATOM 3806 CB   VAL 554  49.472 38.751 -1.802 1.00 26.55
ATOM 3807 CG1  VAL 554  50.696 37.933 -1.418 1.00 23.95
ATOM 3808 CG2  VAL 554  48.953 39.614 -0.682 1.00 25.58
ATOM 3809 C    VAL 554  49.322 41.175 -2.960 1.00 27.53
ATOM 3810 O    VAL 554  48.142 41.502 -3.192 1.00 27.44
ATOM 3811 N    ALA 555  50.277 42.106 -2.716 1.00 28.04
ATOM 3812 H    ALA 555  51.221 41.831 -2.658 1.00  0.00
ATOM 3813 CA   ALA 555  49.956 43.539 -2.509 1.00 28.57
ATOM 3814 CB   ALA 555  51.161 44.427 -2.217 1.00 28.07
```

FIG.5BBB

```
ATOM   3815  C   ALA   555    49.402  44.055  -3.803  1.00 28.12      C
ATOM   3816  O   ALA   555    48.425  44.803  -3.847  1.00 30.12      O
ATOM   3817  N   SER   556    49.985  43.521  -4.839  1.00 26.44      N
ATOM   3818  H   SER   556    50.781  42.956  -4.710  1.00  0.00      H
ATOM   3819  CA  SER   556    49.548  43.810  -6.152  1.00 30.09      C
ATOM   3820  CB  SER   556    50.684  43.277  -6.965  1.00 31.42      C
ATOM   3821  OG  SER   556    50.442  43.338  -8.344  1.00 37.88      O
ATOM   3822  HG  SER   556    49.966  44.144  -8.576  1.00  0.00      H
ATOM   3823  C   SER   556    48.143  43.243  -6.454  1.00 32.78      C
ATOM   3824  O   SER   556    47.287  43.961  -7.003  1.00 34.56      O
ATOM   3825  N   HIS   557    47.750  42.019  -6.088  1.00 32.78      N
ATOM   3826  H   HIS   557    48.350  41.453  -5.560  1.00  0.00      H
ATOM   3827  CA  HIS   557    46.396  41.605  -6.401  1.00 33.64      C
ATOM   3828  CB  HIS   557    46.203  40.142  -6.242  1.00 37.88      C
ATOM   3829  CG  HIS   557    46.986  39.518  -7.348  1.00 42.44      C
ATOM   3830  CD2 HIS   557    46.694  39.665  -8.675  1.00 43.63      C
ATOM   3831  ND1 HIS   557    48.108  38.837  -7.209  1.00 45.23      N
ATOM   3832  HD1 HIS   557    48.641  38.764  -6.385  1.00  0.00      H
ATOM   3833  CE1 HIS   557    48.524  38.569  -8.414  1.00 46.56      C
ATOM   3834  NE2 HIS   557    47.676  39.066  -9.283  1.00 45.62      N
ATOM   3835  HE2 HIS   557    47.793  39.018 -10.257  1.00  0.00      H
ATOM   3836  C   HIS   557    45.383  42.249  -5.520  1.00 32.94      C
ATOM   3837  O   HIS   557    44.256  42.444  -5.934  1.00 33.08      O
ATOM   3838  N   LEU   558    45.744  42.534  -4.280  1.00 33.05      N
ATOM   3839  H   LEU   558    46.657  42.356  -3.986  1.00  0.00      H
ATOM   3840  CA  LEU   558    44.817  43.125  -3.348  1.00 31.91      C
ATOM   3841  CB  LEU   558    45.420  43.107  -1.965  1.00 29.25      C
ATOM   3842  CG  LEU   558    44.605  43.615  -0.818  1.00 26.02      C
ATOM   3843  CD1 LEU   558    43.279  42.883  -0.742  1.00 25.00      C
ATOM   3844  CD2 LEU   558    45.496  43.571   0.408  1.00 22.86      C
ATOM   3845  C   LEU   558    44.527  44.521  -3.783  1.00 32.47      C
ATOM   3846  O   LEU   558    43.402  44.944  -3.596  1.00 33.97      O
ATOM   3847  N   GLN   559    45.482  45.231  -4.370  1.00 34.36      N
ATOM   3848  H   GLN   559    46.386  44.855  -4.406  1.00  0.00      H
ATOM   3849  CA  GLN   559    45.255  46.569  -4.912  1.00 36.75      C
ATOM   3850  CB  GLN   559    46.598  47.067  -5.470  1.00 39.63      C
ATOM   3851  CG  GLN   559    46.707  48.543  -5.875  1.00 42.07      C
ATOM   3852  CD  GLN   559    46.530  49.618  -4.793  1.00 41.53      C
ATOM   3853  OE1 GLN   559    45.961  50.687  -5.057  1.00 41.25      O
ATOM   3854  NE2 GLN   559    46.951  49.416  -3.561  1.00 37.96      N
ATOM   3855  HE21 GLN  559    47.271  48.528  -3.311  1.00  0.00      H
ATOM   3856  HE22 GLN  559    47.001  50.190  -2.967  1.00  0.00      H
ATOM   3857  C   GLN   559    44.142  46.635  -5.976  1.00 35.22      C
ATOM   3858  O   GLN   559    43.165  47.404  -5.839  1.00 34.99      O
ATOM   3859  N   SER   560    44.260  45.817  -7.025  1.00 33.46      N
ATOM   3860  H   SER   560    45.083  45.292  -7.154  1.00  0.00      H
ATOM   3861  CA  SER   560    43.222  45.683  -8.049  1.00 32.88      C
ATOM   3862  CB  SER   560    43.693  44.776  -9.088  1.00 34.05      C
ATOM   3863  OG  SER   560    45.021  45.174  -9.281  1.00 42.40      O
ATOM   3864  HG  SER   560    45.042  45.996  -9.783  1.00  0.00      H
ATOM   3865  C   SER   560    41.885  45.133  -7.559  1.00 32.01      C
ATOM   3866  O   SER   560    40.791  45.582  -7.920  1.00 32.23      O
ATOM   3867  N   PHE   561    41.969  44.123  -6.710  1.00 29.50      N
ATOM   3868  H   PHE   561    42.850  43.767  -6.464  1.00  0.00      H
ATOM   3869  CA  PHE   561    40.803  43.529  -6.118  1.00 28.17      C
ATOM   3870  CB  PHE   561    41.237  42.541  -5.040  1.00 26.27      C
ATOM   3871  CG  PHE   561    40.069  41.966  -4.268  1.00 25.68      C
ATOM   3872  CD1 PHE   561    39.282  40.999  -4.846  1.00 25.44      C
ATOM   3873  CD2 PHE   561    39.761  42.482  -3.051  1.00 25.45      C
ATOM   3874  CE1 PHE   561    38.166  40.551  -4.215  1.00 21.49      C
ATOM   3875  CE2 PHE   561    38.635  42.027  -2.421  1.00 26.89      C
ATOM   3876  CZ  PHE   561    37.853  41.074  -3.008  1.00 24.29      C
ATOM   3877  C   PHE   561    39.987  44.645  -5.505  1.00 28.81      C
ATOM   3878  O   PHE   561    38.789  44.697  -5.731  1.00 29.31      O
ATOM   3879  N   LEU   562    40.672  45.565  -4.797  1.00 28.39      N
ATOM   3880  H   LEU   562    41.643  45.462  -4.707  1.00  0.00      H
ATOM   3881  CA  LEU   562    40.033  46.617  -4.057  1.00 26.51      C
ATOM   3882  CB  LEU   562    40.964  47.203  -3.074  1.00 23.80      C
ATOM   3883  CG  LEU   562    41.047  46.411  -1.816  1.00 24.85      C
ATOM   3884  CD1 LEU   562    42.207  46.868  -1.049  1.00 24.07      C
ATOM   3885  CD2 LEU   562    39.794  46.551  -1.008  1.00 25.13      C
ATOM   3886  C   LEU   562    39.586  47.669  -4.988  1.00 29.27      C
```

FIG.5CCC

```
ATOM 3887 O   LEU 562 38.580 48.304 -4.681 1.00 29.83
ATOM 3888 N   GLU 563 40.239 47.871 -6.115 1.00 30.88
ATOM 3889 H   GLU 563 41.052 47.368 -6.325 1.00 0.00
ATOM 3890 CA  GLU 563 39.738 48.908 -6.966 1.00 36.88
ATOM 3891 CB  GLU 563 40.660 49.142 -8.137 1.00 40.80
ATOM 3892 CG  GLU 563 41.999 49.628 -7.682 1.00 48.55
ATOM 3893 CD  GLU 563 43.148 49.277 -8.619 1.00 55.42
ATOM 3894 OE1 GLU 563 44.301 49.283 -8.135 1.00 57.39
ATOM 3895 OE2 GLU 563 42.886 48.986 -9.808 1.00 56.44
ATOM 3896 C   GLU 563 38.375 48.469 -7.466 1.00 39.02
ATOM 3897 O   GLU 563 37.388 49.170 -7.270 1.00 39.09
ATOM 3898 N   VAL 564 38.289 47.255 -8.030 1.00 42.30
ATOM 3899 H   VAL 564 39.107 46.714 -8.074 1.00 0.00
ATOM 3900 CA  VAL 564 37.052 46.683 -8.558 1.00 41.84
ATOM 3901 CB  VAL 564 37.333 45.255 -9.041 1.00 42.27
ATOM 3902 CG1 VAL 564 36.055 44.538 -9.435 1.00 41.17
ATOM 3903 CG2 VAL 564 38.283 45.348 -10.241 1.00 42.11
ATOM 3904 C   VAL 564 36.030 46.709 -7.442 1.00 41.68
ATOM 3905 O   VAL 564 34.892 47.015 -7.697 1.00 42.34
ATOM 3906 N   SER 565 36.419 46.501 -6.206 1.00 42.75
ATOM 3907 H   SER 565 37.333 46.173 -6.063 1.00 0.00
ATOM 3908 CA  SER 565 35.562 46.602 -5.064 1.00 44.85
ATOM 3909 CB  SER 565 36.344 46.013 -3.894 1.00 46.54
ATOM 3910 OG  SER 565 35.590 45.714 -2.731 1.00 51.75
ATOM 3911 HG  SER 565 35.060 46.481 -2.491 1.00 0.00
ATOM 3912 C   SER 565 35.167 48.063 -4.871 1.00 45.70
ATOM 3913 O   SER 565 34.038 48.287 -4.446 1.00 46.87
ATOM 3914 N   TYR 566 35.965 49.093 -5.146 1.00 47.59
ATOM 3915 H   TYR 566 36.893 48.908 -5.386 1.00 0.00
ATOM 3916 CA  TYR 566 35.518 50.474 -5.086 1.00 49.68
ATOM 3917 CB  TYR 566 36.765 51.362 -5.164 1.00 56.17
ATOM 3918 CG  TYR 566 36.715 52.622 -6.007 1.00 64.64
ATOM 3919 CD1 TYR 566 37.264 52.538 -7.278 1.00 69.53
ATOM 3920 CE1 TYR 566 37.212 53.613 -8.151 1.00 73.71
ATOM 3921 CD2 TYR 566 36.109 53.797 -5.569 1.00 67.98
ATOM 3922 CE2 TYR 566 36.048 54.888 -6.441 1.00 72.92
ATOM 3923 CZ  TYR 566 36.599 54.787 -7.735 1.00 75.29
ATOM 3924 OH  TYR 566 36.538 55.838 -8.652 1.00 77.42
ATOM 3925 HH  TYR 566 36.905 55.565 -9.494 1.00 0.00
ATOM 3926 C   TYR 566 34.524 50.696 -6.217 1.00 48.48
ATOM 3927 O   TYR 566 33.545 51.376 -5.950 1.00 46.35
ATOM 3928 N   ALA 567 34.679 50.115 -7.417 1.00 49.14
ATOM 3929 H   ALA 567 35.512 49.625 -7.572 1.00 0.00
ATOM 3930 CA  ALA 567 33.670 50.165 -8.490 1.00 52.09
ATOM 3931 CB  ALA 567 34.210 49.574 -9.788 1.00 48.37
ATOM 3932 C   ALA 567 32.315 49.449 -8.238 1.00 55.31
ATOM 3933 O   ALA 567 31.226 50.008 -8.501 1.00 56.87
ATOM 3934 N   VAL 568 32.247 48.211 -7.736 1.00 57.66
ATOM 3935 H   VAL 568 33.083 47.729 -7.564 1.00 0.00
ATOM 3936 CA  VAL 568 30.980 47.573 -7.490 1.00 59.61
ATOM 3937 CB  VAL 568 31.119 46.031 -7.339 1.00 58.96
ATOM 3938 CG1 VAL 568 31.239 45.508 -5.911 1.00 60.27
ATOM 3939 CG2 VAL 568 29.851 45.471 -7.922 1.00 60.44
ATOM 3940 C   VAL 568 30.393 48.177 -6.245 1.00 62.66
ATOM 3941 O   VAL 568 29.174 48.154 -6.180 1.00 64.78
ATOM 3942 N   LEU 569 31.075 48.737 -5.248 1.00 66.15
ATOM 3943 H   LEU 569 32.058 48.719 -5.243 1.00 0.00
ATOM 3944 CA  LEU 569 30.359 49.334 -4.123 1.00 69.85
ATOM 3945 CB  LEU 569 31.285 49.858 -3.023 1.00 69.91
ATOM 3946 CG  LEU 569 32.007 48.887 -2.095 1.00 70.17
ATOM 3947 CD1 LEU 569 32.847 49.687 -1.140 1.00 70.19
ATOM 3948 CD2 LEU 569 31.039 48.054 -1.286 1.00 70.56
ATOM 3949 C   LEU 569 29.567 50.509 -4.667 1.00 72.69
ATOM 3950 O   LEU 569 28.365 50.553 -4.425 1.00 73.80
ATOM 3951 N   ARG 570 30.180 51.391 -5.479 1.00 75.95
ATOM 3952 H   ARG 570 31.153 51.299 -5.580 1.00 0.00
ATOM 3953 CA  ARG 570 29.510 52.498 -6.173 1.00 78.78
ATOM 3954 CB  ARG 570 30.399 53.068 -7.308 1.00 80.07
ATOM 3955 CG  ARG 570 29.658 54.222 -7.997 1.00 84.16
ATOM 3956 CD  ARG 570 29.976 54.744 -9.417 1.00 85.66
ATOM 3957 NE  ARG 570 28.892 55.690 -9.737 1.00 85.67
ATOM 3958 HE  ARG 570 27.971 55.354 -9.727 1.00 0.00
```

FIG.5DDD

```
ATOM 3959 CZ   ARG 570   29.051 56.991 -10.026 1.00 85.06  C
ATOM 3960 NH1  ARG 570   30.240 57.590 -10.082 1.00 84.43  C
ATOM 3961 HH11 ARG 570   31.069 57.056  -9.908 1.00  0.00  C
ATOM 3962 HH12 ARG 570   30.295 58.561 -10.314 1.00  0.00  C
ATOM 3963 NH2  ARG 570   27.958 57.736 -10.154 1.00 84.57  C
ATOM 3964 HH21 ARG 570   27.059 57.316 -10.030 1.00  0.00  C
ATOM 3965 HH22 ARG 570   28.042 58.708 -10.375 1.00  0.00  C
ATOM 3966 C    ARG 570   28.201 52.009  -6.812 1.00 79.92  C
ATOM 3967 O    ARG 570   27.107 52.565  -6.709 1.00 79.61  C
ATOM 3968 N    HIS 571   28.362 50.900  -7.511 1.00 81.35  C
ATOM 3969 H    HIS 571   29.214 50.417  -7.440 1.00  0.00  C
ATOM 3970 CA   HIS 571   27.247 50.306  -8.197 1.00 82.75  C
ATOM 3971 CB   HIS 571   27.882 49.274  -9.167 1.00 83.42  C
ATOM 3972 CG   HIS 571   28.633 50.029 -10.280 1.00 85.08  C
ATOM 3973 CD2  HIS 571   28.921 49.529 -11.532 1.00 85.81  C
ATOM 3974 ND1  HIS 571   29.074 51.303 -10.268 1.00 86.25  C
ATOM 3975 HD1  HIS 571   29.080 51.900  -9.489 1.00  0.00  C
ATOM 3976 CE1  HIS 571   29.595 51.595 -11.439 1.00 86.01  C
ATOM 3977 NE2  HIS 571   29.494 50.518 -12.187 1.00 86.28  C
ATOM 3978 HE2  HIS 571   29.801 50.468 -13.119 1.00  0.00  C
ATOM 3979 C    HIS 571   26.225 49.759  -7.195 1.00 83.31  C
ATOM 3980 O    HIS 571   25.075 50.194  -7.301 1.00 84.06  C
ATOM 3981 N    LEU 572   26.540 48.963  -6.158 1.00 83.11  C
ATOM 3982 H    LEU 572   27.474 48.824  -5.915 1.00  0.00  C
ATOM 3983 CA   LEU 572   25.527 48.457  -5.241 1.00 83.71  C
ATOM 3984 CB   LEU 572   26.085 47.267  -4.454 1.00 83.57  C
ATOM 3985 CG   LEU 572   25.439 45.884  -4.721 1.00 83.79  C
ATOM 3986 CD1  LEU 572   25.783 45.386  -6.127 1.00 84.16  C
ATOM 3987 CD2  LEU 572   25.958 44.866  -3.714 1.00 84.08  C
ATOM 3988 C    LEU 572   24.997 49.511  -4.261 1.00 84.78  C
ATOM 3989 O    LEU 572   24.265 49.192  -3.295 1.00 84.85  C
ATOM 3990 N    ALA 573   25.349 50.796  -4.483 1.00 85.56  C
ATOM 3991 H    ALA 573   26.020 50.980  -5.174 1.00  0.00  C
ATOM 3992 CA   ALA 573   24.822 51.925  -3.721 1.00 85.90  C
ATOM 3993 CB   ALA 573   25.600 53.207  -3.970 1.00 85.79  C
ATOM 3994 C    ALA 573   23.373 52.245  -4.057 1.00 87.21  C

ATOM 3995 OT1  ALA 573   22.610 52.413  -3.099 1.00 88.33  O
ATOM 3996 OT2  ALA 573   23.022 52.309  -5.248 1.00 88.34  W
ATOM 3997 OH2  H2O 603   26.735 24.280   5.161 1.00 27.42  W
ATOM 3998 H1   H2O 603   27.332 24.335   4.407 1.00  0.00  W
ATOM 3999 H2   H2O 603   26.288 23.435   4.992 1.00  0.00  W
ATOM 4000 OH2  H2O 605   47.880 37.960  12.073 1.00 56.30  W
ATOM 4001 H1   H2O 605   47.789 37.874  13.031 1.00  0.00  W
ATOM 4002 H2   H2O 605   46.980 37.858  11.753 1.00  0.00  W
ATOM 4003 OH2  H2O 607   40.001 49.224   7.214 1.00 40.04  W
ATOM 4004 H1   H2O 607   40.471 48.761   7.909 1.00  0.00  W
ATOM 4005 H2   H2O 607   40.123 48.642   6.457 1.00  0.00  W
ATOM 4006 OH2  H2O 610   59.883 42.530  -9.698 1.00 38.90  W
ATOM 4007 H1   H2O 610   60.512 41.833  -9.477 1.00  0.00  W
ATOM 4008 H2   H2O 610   59.189 42.046 -10.160 1.00  0.00  W
ATOM 4009 OH2  H2O 611   57.178 35.940 -14.220 1.00 34.63  W
ATOM 4010 H1   H2O 611   57.174 36.545 -14.974 1.00  0.00  W
ATOM 4011 H2   H2O 611   57.989 36.211 -13.757 1.00  0.00  W
ATOM 4012 OH2  H2O 612   25.793 27.337  19.130 1.00 29.21  W
ATOM 4013 H1   H2O 612   26.709 27.661  19.145 1.00  0.00  W
ATOM 4014 H2   H2O 612   25.762 26.792  19.929 1.00  0.00  W
ATOM 4015 OH2  H2O 615   29.766 34.284   9.444 1.00 45.03  W
ATOM 4016 H1   H2O 615   30.017 34.618  10.308 1.00  0.00  W
ATOM 4017 H2   H2O 615   29.113 33.592   9.660 1.00  0.00  W
ATOM 4018 OH2  H2O 617   37.316 40.012  10.872 1.00 35.21  W
ATOM 4019 H1   H2O 617   36.600 40.017  11.519 1.00  0.00  W
ATOM 4020 H2   H2O 617   37.944 39.376  11.259 1.00  0.00  W
ATOM 4021 OH2  H2O 619   40.370 52.041  -7.387 1.00 29.62  W
ATOM 4022 H1   H2O 619   40.672 52.724  -6.779 1.00  0.00  W
ATOM 4023 H2   H2O 619   39.505 51.810  -7.052 1.00  0.00  W
ATOM 4024 OH2  H2O 621   27.903 32.440  10.664 1.00 39.99  W
ATOM 4025 H1   H2O 621   27.553 33.207  11.141 1.00  0.00  W
ATOM 4026 H2   H2O 621   27.929 31.808  11.398 1.00  0.00  W
ATOM 4027 OH2  H2O 622   25.057 31.972  13.675 1.00 32.70  W
ATOM 4028 H1   H2O 622   24.393 32.417  14.215 1.00  0.00  W
ATOM 4029 H2   H2O 622   24.469 31.428  13.112 1.00  0.00  W
ATOM 4030 OH2  H2O 623   20.791 28.583  14.218 1.00 50.17  W
```

FIG.5EEE

```
ATOM 4031 H1  H2O 623  20.499 28.803 13.325  1.00  0.00 W
ATOM 4032 H2  H2O 623  19.939 28.549 14.688  1.00  0.00 W
ATOM 4033 OH2 H2O 625  22.680 78.881  2.761  1.00 40.48 W
ATOM 4034 H1  H2O 625  21.938 78.856  3.375  1.00  0.00 W
ATOM 4035 H2  H2O 625  22.266 79.246  1.970  1.00  0.00 W
ATOM 4036 OH2 H2O 626  39.689 36.486  9.730  1.00 23.36 W
ATOM 4037 H1  H2O 626  39.090 35.724  9.672  1.00  0.00 W
ATOM 4038 H2  H2O 626  39.627 36.872  8.853  1.00  0.00 W
ATOM 4039 OH2 H2O 627  42.035 78.320  5.697  1.00 46.19 W
ATOM 4040 H1  H2O 627  42.416 77.450  5.832  1.00  0.00 W
ATOM 4041 H2  H2O 627  41.243 78.146  5.181  1.00  0.00 W
ATOM 4042 OH2 H2O 631  47.227 31.440  6.299  1.00 34.17 W
ATOM 4043 H1  H2O 631  47.533 32.209  5.809  1.00  0.00 W
ATOM 4044 H2  H2O 631  47.442 30.713  5.714  1.00  0.00 W
ATOM 4045 OH2 H2O 636  24.043 65.423 -0.336  1.00 73.38 W
ATOM 4046 H1  H2O 636  24.179 65.781 -1.228  1.00  0.00 W
ATOM 4047 H2  H2O 636  23.469 66.096  0.054  1.00  0.00 W
ATOM 4048 OH2 H2O 638  38.984 67.955 -11.226 1.00 29.97 W
ATOM 4049 H1  H2O 638  38.283 67.402 -11.580 1.00  0.00 W
ATOM 4050 H2  H2O 638  39.568 68.046 -11.998 1.00  0.00 W
ATOM 4051 OH2 H2O 639  27.930 66.675 -7.733  1.00 43.40 W
ATOM 4052 H1  H2O 639  28.192 67.028 -6.876  1.00  0.00 W
ATOM 4053 H2  H2O 639  26.975 66.791 -7.705  1.00  0.00 W
ATOM 4054 OH2 H2O 643  50.619 62.802  0.813  1.00 36.55 W
ATOM 4055 H1  H2O 643  51.575 62.904  0.824  1.00  0.00 W
ATOM 4056 H2  H2O 643  50.301 63.665  0.525  1.00  0.00 W
ATOM 4057 OH2 H2O 646  62.897 38.367  3.759  1.00 73.55 W
ATOM 4058 H1  H2O 646  62.414 38.098  2.978  1.00  0.00 W
ATOM 4059 H2  H2O 646  62.244 38.247  4.461  1.00  0.00 W
ATOM 4060 OH2 H2O 650  29.587 68.480 -9.555  1.00 65.67 W
ATOM 4061 H1  H2O 650  28.846 68.630 -10.148 1.00  0.00 W
ATOM 4062 H2  H2O 650  29.180 67.844 -8.936  1.00  0.00 W
ATOM 4063 OH2 H2O 652  51.408 56.331  4.056  1.00 62.90 W
ATOM 4064 H1  H2O 652  50.718 56.353  3.365  1.00  0.00 W
ATOM 4065 H2  H2O 652  51.052 55.671  4.648  1.00  0.00 W
ATOM 4066 OH2 H2O 653  49.404 56.022  2.161  1.00 51.28 W

ATOM 4067 H1  H2O 653  49.442 55.351  1.474  1.00  0.00 W
ATOM 4068 H2  H2O 653  49.323 56.829  1.630  1.00  0.00 W
ATOM 4069 OH2 H2O 654  68.215 42.294 -2.563  1.00 40.77 W
ATOM 4070 H1  H2O 654  68.347 41.745 -1.777  1.00  0.00 W
ATOM 4071 H2  H2O 654  68.189 43.181 -2.190  1.00  0.00 W
ATOM 4072 OH2 H2O 655  66.374 40.425 -2.489  1.00 42.31 W
ATOM 4073 H1  H2O 655  66.936 41.162 -2.766  1.00  0.00 W
ATOM 4074 H2  H2O 655  66.452 39.841 -3.252  1.00  0.00 W
ATOM 4075 OH2 H2O 656  66.927 41.428 -5.011  1.00 44.08 W
ATOM 4076 H1  H2O 656  66.207 42.071 -4.989  1.00  0.00 W
ATOM 4077 H2  H2O 656  67.542 41.824 -4.374  1.00  0.00 W
ATOM 4078 OH2 H2O 657  40.371 57.111  5.730  1.00 66.56 W
ATOM 4079 H1  H2O 657  39.958 56.259  5.613  1.00  0.00 W
ATOM 4080 H2  H2O 657  40.021 57.651  5.014  1.00  0.00 W
ATOM 4081 OH2 H2O 658  48.780 47.580 -3.122  1.00 52.09 W
ATOM 4082 H1  H2O 658  48.811 46.671 -3.438  1.00  0.00 W
ATOM 4083 H2  H2O 658  49.568 47.955 -3.542  1.00  0.00 W
ATOM 4084 OH2 H2O 663  29.095 62.889  1.825  1.00 39.23 W
ATOM 4085 H1  H2O 663  29.380 62.827  2.739  1.00  0.00 W
ATOM 4086 H2  H2O 663  28.377 63.526  1.887  1.00  0.00 W
ATOM 4087 OH2 H2O 664  27.132 25.640  7.430  1.00 50.65 W
ATOM 4088 H1  H2O 664  26.870 24.838  7.876  1.00  0.00 W
ATOM 4089 H2  H2O 664  27.001 25.362  6.496  1.00  0.00 W
ATOM 4090 OH2 H2O 665  23.367 30.554 12.167  1.00 49.69 W
ATOM 4091 H1  H2O 665  24.026 30.006 11.707  1.00  0.00 W
ATOM 4092 H2  H2O 665  22.941 31.016 11.438  1.00  0.00 W
ATOM 4093 OH2 H2O 666  46.015 32.192 10.179  1.00 66.86 W
ATOM 4094 H1  H2O 666  46.060 31.519  9.497  1.00  0.00 W
ATOM 4095 H2  H2O 666  45.411 31.827 10.833  1.00  0.00 W
ATOM 4096 OH2 H2O 667  38.943 37.883 11.978  1.00 47.87 W
ATOM 4097 H1  H2O 667  39.367 37.487 11.188  1.00  0.00 W
ATOM 4098 H2  H2O 667  38.521 37.114 12.362  1.00  0.00 W
ATOM 4099 OH2 H2O 671  33.437 58.101  2.269  1.00 46.65 W
ATOM 4100 H1  H2O 671  33.555 57.162  2.433  1.00  0.00 W
ATOM 4101 H2  H2O 671  33.962 58.514  2.961  1.00  0.00 W
ATOM 4102 OH2 H2O 672  27.551 31.314 20.022  1.00 30.15 W
```

FIG.5FFF

ATOM	4103	H1	H2O	672	27.929	32.042	20.533	1.00 0.00	W
ATOM	4104	H2	H2O	672	26.845	31.764	19.552	1.00 0.00	W
ATOM	4105	OH2	H2O	673	25.714	36.908	21.385	1.00 36.95	W
ATOM	4106	H1	H2O	673	24.806	37.123	21.637	1.00 0.00	W
ATOM	4107	H2	H2O	673	25.599	36.284	20.654	1.00 0.00	W
ATOM	4108	OH2	H2O	674	38.244	66.897	12.076	1.00 57.36	W
ATOM	4109	H1	H2O	674	37.773	67.536	12.626	1.00 0.00	W
ATOM	4110	H2	H2O	674	38.153	66.104	12.618	1.00 0.00	W
ATOM	4111	OH2	H2O	675	35.762	36.553	-3.986	1.00 58.40	W
ATOM	4112	H1	H2O	675	35.600	37.449	-3.677	1.00 0.00	W
ATOM	4113	H2	H2O	675	35.549	36.642	-4.923	1.00 0.00	W
ATOM	4114	OH2	H2O	676	30.689	32.814	25.675	1.00 59.30	W
ATOM	4115	H1	H2O	676	30.093	33.571	25.680	1.00 0.00	W
ATOM	4116	H2	H2O	676	31.550	33.214	25.540	1.00 0.00	W
END									
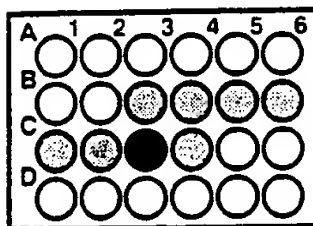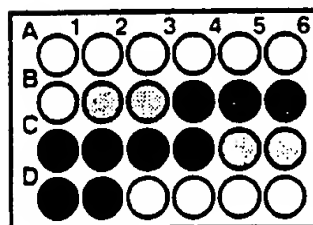
FIG. 6A

FIG. 6B

FIG. 6C

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5   C12N15/27   C07K3/00   C12P21/02   C07K13/00   G06F15/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5   C12N   C07K   C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DISSERTATION ABSTRACTS INTERNATIONAL B. vol. 54, no. 3 , September 1993 page 1239 T. OSSLUND ET AL 'The structure of granulocyte-colony stimulating factor' see abstract ---	1-8
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA vol. 90 , June 1993 , WASHINGTON US pages 5167 - 5171 C.P. HILL ET AL 'The structure of Granulocyte-colony-stimulating factor and its relationship to other growth factors' see the whole document --- -/--	1-8

[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 1994	0 1 -06- 1994

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Le Cornec, N

Form PCT/ISA/210 (second sheet) (July 1992)

page 1 of 3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL STRUCTURE AND FUNCTION vol. 17, no. 1 , February 1992 pages 61 - 65 MASAHARU ISHIKAWA ET AL 'The sustitution of Cysteine 17 of recombinant human G-CSF with Alanine greatly enhanced its stability' see the whole document ---	43
X	WO,A,87 01132 (KIRIN-AMGEN, INC.) 26 February 1987 see claims; examples 7-9 & US,A,4 810 643 (KIRIN-AMGEN, INC.) 7 March 1989 cited in the application ---	9
X	WO,A,89 05824 (GENETICS INSTITUTE, INC.) 29 June 1989 * see the whole document especially page 17 table 2 , page 21 lines 16-19 and page 22 lines 25-37 * & US,A,4 904 584 (GENETICS INSTITUTE) 27 February 1990 cited in the application ---	17-22
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 159, no. 1 , 28 February 1989 , DULUTH, MINNESOTA US pages 103 - 111 TETSURO KUGA ET AL 'Mutagenesis of human granulocyte colony stimulating factor' cited in the application see the whole document ---	9-59
Y	EP,A,0 344 796 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 6 December 1989 cited in the application see the whole document --- -	1-8
Y	BIOCHEMISTRY vol. 30 , 1991 , EASTON, PA US pages 4151 - 4159 L. ABRAHMSEN ET AL 'Engineering subtilisin and its sustrates for efficient ligation of peptide bonds in aqueous solution' * see the whole document especially page 4152 right column , page 4153 right column and the discussion * ---	1-8

2

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCIENCE vol. 258 , 20 November 1992 , LANCASTER, PA US pages 1358 - 1362 J. PANDIT ET AL 'Three-dimensional Structure of dimeric human recombinant Macrophage Colony-Stimulating Factor' cited in the application see the whole document ---	1-8
P,A	WO,A,93 25687 (CHIRON CORPORATION) 23 December 1993 see page 16, line 11 - page 17, line 5 see examples 1,9,10,11,13 see appendix 1 see claims ---	1-8
P,X	JOURNAL OF CELLULAR BIOCHEMISTRY SUPPL 0 no. 17B , 26 JANUARY-10 FEBRUARY 1993 page 78 J. E. LAYTON ET AL 'Interaction of G-CSF with its receptor : Dissociation of biological activity and Receptor binding' * see abstract E 225 * ---	27,32, 34-38, 51-53
A	EP,A,0 456 200 (BOEHRINGER MANNHEIM GMBH) 13 November 1991 ---	
A	JOURNAL OF APPLIED CRYSTALLOGRAPHY vol. 20 , 1987 pages 366 - 373 M.J. COX ET AL 'Experiments with automated protein crystallization' cited in the application ---	
T	POUR LA SCIENCE vol. 183 , January 1993 pages 76 - 82 A. OLSON ET AL 'Voir les Molécules biologiques' ---	
Y	PROTEIN ENGINEERING 1987 , ALAN R. LISS, INC. pages 35 - 44 M. KARPLUS 'The prediction and Analysis of mutant strutures' see the whole document ---	1-8
A	WO,A,88 01775 (GENEX CORPORATION) 10 March 1988 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8701132	26-02-87	US-A- 4810643	07-03-89
		AU-A- 6334686	10-03-87
		AU-A- 6937391	02-05-91
		EP-A,B 0237545	23-09-87
		EP-A- 0396158	07-11-90
		JP-A- 2042998	13-02-90
		JP-C- 1729335	29-01-93
		JP-A- 2031675	01-02-90
		JP-B- 4002599	20-01-92
		JP-A- 6090751	05-04-94
		JP-B- 3031437	07-05-91
		JP-T- 63500636	10-03-88
		US-A- 4999291	12-03-91
		BG-A- 60169	15-11-93
US-A-4810643	07-03-89	AU-A- 6334686	10-03-87
		BG-A- 60169	15-11-93
		EP-A,B 0237545	23-09-87
		EP-A- 0396158	07-11-90
		JP-A- 2042998	13-02-90
		JP-C- 1729335	29-01-93
		JP-A- 2031675	01-02-90
		JP-B- 4002599	20-01-92
		JP-A- 6090751	05-04-94
		WO-A- 8701132	26-02-87
		AU-A- 6937391	02-05-91
		JP-B- 3031437	07-05-91
		JP-T- 63500636	10-03-88
		US-A- 4999291	12-03-91
WO-A-8905824	29-06-89	US-A- 4904584	27-02-90
		AU-A- 2911189	19-07-89
		EP-A- 0355142	28-02-90
US-A-4904584	27-02-90	AU-A- 2911189	19-07-89
		EP-A- 0355142	28-02-90
		WO-A- 8905824	29-06-89
EP-A-0344796	06-12-89	JP-A- 2209895	21-08-90

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9325687	23-12-93	NONE		
EP-A-0456200	13-11-91	DE-A-	4014750	14-11-91
		AU-B-	631312	19-11-92
		AU-A-	7638091	14-11-91
		CN-A-	1057862	15-01-92
		JP-A-	4225998	14-08-92
		KR-B-	9400757	29-01-94
WO-A-8801775	10-03-88	US-A-	4704692	03-11-87
		EP-A-	0279848	31-08-88
		US-A-	4881175	14-11-89